



Critical Care Reviews Book 2017

The Biggest Trials of 2016



**Critical Care
Reviews**



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Critical Care Reviews



About

The 2017 Critical Care Reviews Book seeks to summarise, critique and put in context the best critical care trials of 2016. Five intensivists working in Northern Ireland have spent the past year writing this edition.

Our choices are largely subjective and clearly some major studies may have been excluded, but we feel we have captured the essence of the critical care research output from the past 12 months. We hope you enjoy this work and find it useful in your daily practice. Please read the disclaimer at the bottom of this page.

The print version of the book has been very generously sponsored by the REVIVE charity of the Regional Intensive Care at the Royal Victoria Hospital in Belfast, where two of the authors work. Every registered delegate at the annual Critical Care Reviews Meeting receives a complimentary copy. The pdf is available as a free download at the Critical Care Reviews website, www.criticalcarereviews.com

We would love to hear any feedback you may have on this book. All correspondence will be gratefully received at rob@criticalcarereviews.com

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Belfast, January 2017

Disclaimer:

This book aims to summarise the major critical care trials of 2016. Although care has been taken to ensure information is correct, this is not guaranteed and no responsibility is accepted for clinical decisions based on material within this book. Clinicians are advised to check the primary literature at all times. The opinions stated within this book do not constitute clinical advice. They are opinions, not fact, and others may take a different view of our interpretations of these trials. Please refer to the appropriate clinical guideline issued by the relevant society or scientific body for the management of any specific condition.

Critical Care Reviews



Foreword

There are at least 50,000 randomised controlled trials (RCTs) published each year and the doubling time for the number of RCTs is estimated to be between 7 and 10 years. Although only a small proportion of the trials and research papers published relate to critical care, the volume of new knowledge and data (at least 100 papers per week) far exceeds that which any individual could speed read, far less critically review, assimilate or truly understand.



For busy clinicians the challenge of how to remain up to date and how to decide which new studies or trials should change their clinical practice is very real. It is not just the challenge provided by the sheer volume of data but also being honest with one self about whether you have the methodological skills to know whether a particular piece of work, no matter how attractive the results may seem and how strongly they support your pre-existing bias, is robust enough to consider changing your clinical practice. This book, which provides a reference work for the Critical Care Reviews meeting, and which summarizes and critiques the biggest critical care trials of 2016, is an invaluable resource to help with that challenge.

Reading this book can't fail to assist you in treating your patients. Even better is if you are reading this book as one of the attendees at the Critical Care Reviews Meeting held in Belfast in January 2017. The meeting will have given you the opportunity to hear and question the researchers who conducted the studies described in this book. No-one has better insight into the true meaning of a piece of research than those who conducted it and that insight can often illuminate the dry and often unnecessarily complex publication and presentation of research data. Researchers are often accused of overstating the importance and significance of their work and at times this accusation is justified, but an honest researcher will also be able to articulate their study's weaknesses and the strength or otherwise of the inferences drawn from the results.

The Critical Care Reviews Meeting and this book provides a unique opportunity to share in those insights. I commend both the meeting and the book to you.

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Table of Contents

| | |
|--|-----|
| The Best Critical Care Trials of 2016..... | 1 |
| Neuro Trials..... | 2 |
| RESCUEicp..... | 3 |
| HYBERNATUS..... | 9 |
| Dexmedetomidine for Delirium in Non-Cardiac Surgery..... | 16 |
| Light Therapy for Delirium..... | 23 |
| Circulatory Trials..... | 29 |
| ALPS..... | 30 |
| RINSE..... | 37 |
| CYRUS..... | 46 |
| CCC..... | 54 |
| Respiratory Trials..... | 62 |
| High-Flow Nasal Oxygen vs Facemask Oxygen post-extubation..... | 63 |
| High-Flow Nasal Oxygen vs NIV post-extubation..... | 73 |
| OPERA..... | 82 |
| NIVAS..... | 91 |
| HELMET NIV..... | 100 |
| LIPS-A..... | 107 |
| Oxygen-ICU..... | 115 |
| CLOSE..... | 122 |
| DIABOLO..... | 130 |
| Rehabilitation in Acute Respiratory Failure..... | 136 |
| IPHIVAP..... | 145 |
| LUNG SAFE..... | 154 |
| GI & Nutrition Trials..... | 162 |
| PEPaNIC..... | 163 |
| POP-UP..... | 171 |
| Renal Trials..... | 177 |
| AKIKI..... | 178 |
| ELAIN..... | 186 |
| Haematology Trials..... | 196 |
| IRONMAN..... | 197 |
| Sepsis Trials..... | 203 |
| SEPSIS 3..... | 204 |
| LeoPARDS..... | 212 |
| VANISH..... | 219 |
| CLASSIC..... | 227 |
| EMPIRICUS..... | 234 |
| SISPCT..... | 243 |
| Protein C Zymogen..... | 250 |



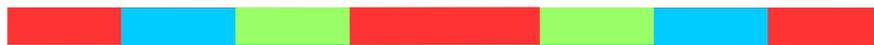
| | |
|--|-----|
| SMOOTH..... | 258 |
| MARS..... | 264 |
| Miscellaneous Trials..... | 271 |
| REACT-2..... | 272 |
| Early Mobilisation..... | 281 |
| CHECKLIST-ICU..... | 288 |
| Surrogate Decision Maker..... | 295 |
| PALLIATIVE CARE..... | 301 |
| The Best of the Rest..... | 307 |
| The Best of the Rest: NEURO..... | 308 |
| ATACH-2..... | 308 |
| DahLIA..... | 309 |
| SEGA..... | 310 |
| PremaTOR..... | 311 |
| PATCH..... | 312 |
| The Best of the Rest: CIRCULATORY..... | 313 |
| Chest Compression Rates..... | 313 |
| HYPRESS..... | 314 |
| Corticosteroid Therapy in Refractory Shock Following Cardiac Arrest..... | 315 |
| OVATION..... | 316 |
| Prophylactic Antibiotics after Out-of-Hospital Cardiac Arrest..... | 317 |
| ADVANCED..... | 318 |
| EPO-ACR-02..... | 319 |
| GLIP1..... | 320 |
| Statin AKI Cardiac Surgery Trial..... | 321 |
| The Best of the Rest: RESPIRATORY..... | 322 |
| OPTINIV..... | 322 |
| TRACHUS..... | 323 |
| Steroids in ARDS..... | 324 |
| IASIS..... | 325 |
| Probiotics for the Prevention of VAP..... | 326 |
| EVDCPR..... | 327 |
| NAVA vs Pressure Support..... | 328 |
| The Best of the Rest: HEPATOBILARY..... | 329 |
| Terlipressin vs Noradrenaline in Cirrhotic Septic Shock..... | 329 |
| The Best of the Rest: RENAL..... | 330 |
| SALT..... | 330 |
| The Best of the Rest: METABOLIC..... | 331 |
| Thiamine in Septic Shock..... | 331 |
| The Best of the Rest: HAEMATOLOGY..... | 332 |
| INFORM..... | 332 |
| The Best of the Rest: SEPSIS..... | 333 |



| | |
|--|-----|
| Dopamine vs Adrenaline in Paediatric Septic Shock..... | 333 |
| The Best of the Rest: MISCELLANEOUS..... | 334 |
| ICU Family Communication Study..... | 334 |
| RAPIT..... | 335 |
| Fragility Index..... | 336 |
| The Best Non-Paywalled Guidelines of 2016..... | 337 |
| The Best Guidelines: AIRWAY..... | 338 |
| The Best Guidelines: NEURO..... | 338 |
| The Best Guidelines: CIRCULATORY..... | 339 |
| The Best Guidelines: RESPIRATORY..... | 340 |
| The Best Guidelines: GI & NUTRITION..... | 340 |
| The Best Guidelines: HEPATOBILARY..... | 341 |
| The Best Guidelines: RENAL..... | 341 |
| The Best Guidelines: ENDOCRINE..... | 342 |
| The Best Guidelines: METABOLIC..... | 342 |
| The Best Guidelines: HAEMATOLOGY..... | 342 |
| The Best Guidelines: SEPSIS..... | 342 |
| The Best Guidelines: TRAUMA..... | 343 |
| The Best Guidelines: BURNS..... | 344 |
| The Best Guidelines: TOXICOLOGY..... | 344 |
| The Best Guidelines: PAEDIATRICS..... | 344 |
| The Best Guidelines: MISCELLANEOUS..... | 344 |



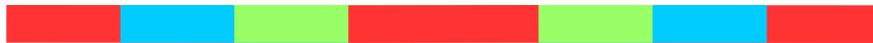
Section 1



The Best Critical Care Trials of 2016



Neuro Trials



RESCUEicp

Hutchinson PJ, Koliaf AJ, Timofeev IS, Corteen AE, Czosnyka M, Timothy J et al. Trial of Decompressive Craniectomy for Traumatic Intra-cranial Hypertension. *N Engl J Med* 2016; 375:1119-1130

Introduction

Traumatic brain injury (TBI) is a major global public health and socioeconomic concern.¹ Although epidemiological figures are difficult to interpret, due to differences in coding and recording of hospital admissions between countries, European data suggests an estimated 20 admissions per 100,000 population require neurosurgical management.² Mortality from severe TBI is currently 30% to 40%.¹ More people than ever are living with the physical, cognitive and psychological challenges of TBI survival. Approximately 60% of survivors have an unfavourable outcome on the Glasgow Outcome Score.³ Lifetime costs are estimated at US \$400,000, with 80% accounted for by disability and lost productivity.⁴

One of the challenges in the critical care management of TBI is the translation of targeted physiological variables to meaningful patient-centred outcomes. Although the BEST-TRIP trial challenges the paradigm of invasive ICP monitoring to guide treatment interventions, it is likely ICP monitoring will remain central to the management of TBI in developed countries because of the lack of equipoise that exists.⁵

The recently published 4th edition of the Brain Trauma Foundation TBI management guideline has summarised the evidence in this field. One class I trial and two class II trials contribute to current recommendations for decompressive craniectomy. The seven class III studies (prospective and retrospective cohort and observational studies) were deemed to be of insufficient quality on which to base recommendations.⁶

The DECRA trial demonstrated patients with diffuse TBI randomised to early decompressive craniectomy had a more unfavourable 6 month Extended Glasgow Outcome Score (GOS-E) than those randomised to standard care. Furthermore, the complication rate was higher among the intervention group.⁷ Against this backdrop, and with some methodological differences, the RESCUEicp trial was conducted with the aim of clarifying the role of decompressive craniectomy in the management of severe TBI.

Study synopsis

RESCUEicp was a multi-centre, parallel group, randomised-controlled trial which recruited patients over a 10 year period from 2004 to 2014. The aim was to determine whether patients who had suffered a TBI and had refractory intra-cranial hypertension, had a more favourable GOS-E at 6 months if they were managed with secondary decompressive craniectomy or with continued medical management, which was



predominantly barbiturate therapy. The intervention was applied as a stage 3 measure.

Refractory intra-cranial hypertension was defined as an ICP \geq 25 mm Hg for 1 to 12 hours despite the implementation of stage 1 (sedation & analgesia, mechanical ventilation, paralysis, head-up positioning) and stage 2 (ventriculostomy, osmotherapy, loop diuretics, inotropes, hypothermia) interventions. Patients with fixed dilated pupils, bleeding diathesis or who had suffered an injury deemed to be unsurvivable were excluded. Although 71% of patients were recruited from UK intensive care units, 52 ICUs in 20 countries randomised patients. Using a central telephone randomisation service, randomisation was in a 1:1 ratio using permuted blocks of random sizes and was stratified according to site. The surgical technique for the decompressive craniectomy was left to the discretion of the operating surgeon. The primary outcome measure was GOS-E at 6 months. Secondary outcome measures included GOS-E at 12 and 24 months, as well as mortality and quality of life at 6, 12 and 24 months. Allowing for a 15% loss to follow-up, 400 patients were required to detect a 15% absolute improvement in the primary outcome, from 60% to 45%, with 80% power and at a 5% significance level.

Of 2008 patients assessed, 408 patients (20%) were randomised - 206 to the craniectomy group and 202 to the medical group. Most patients were excluded due to an absence of intra-cranial hypertension (37.5%), had already undergone a primary decompressive craniectomy (15%), had either fixed dilated pupils (6.8%) or were deemed to have an unsurvivable injury (8%). Two hundred and two patients in the surgical group and 196 in the medical group were analysed for the primary outcome using a modified intention-to-treat analysis.

Drug and alcohol misuse was higher in the medical group (35.2% vs 24.8%) but groups were otherwise well matched for baseline characteristics. No significant between-group differences were observed before randomisation in stage 1 or stage 2 interventions. 92.6% (n=187) of patients randomised to surgery underwent a decompressive craniectomy. Of those randomised to medical treatment, 87.2% (n=171) received barbiturates. Crossover occurred in both groups, with 37.2% of those in the medical group eventually receiving a decompressive craniectomy and 9.4% of those in the surgical group receiving barbiturates in addition to decompression. The surgical group had a significantly lower median (IQR) ICP after randomisation compared to the medical group, 14.5 mm Hg (1.7 to 18.0) vs 17.1 mm Hg (4.2 to 21.8); difference -3.0 mm Hg, 95% CI, -4.1 to -1.8); $P < 0.001$.

As Table 1 illustrates, the primary outcome measure of GOS-E at 6 months showed a higher proportion of patients in the surgical group survived in a vegetative state and lower severe disability compared to the medical group. Those surviving with upper severe disability, a favourable outcome, were more numerous in the surgical group at 6 months. Overall, favourable outcomes occurred in 42.8% vs 34.6% in the surgical vs



medical groups respectively (P=0.12) at 6 months.

| GOS-E | 6 Months (%) | | 12 Months (%) | | |
|---------------------------|------------------|-----------------|------------------|-----------------|---------------------|
| | Surgical (N=201) | Medical (N=188) | Surgical (N=194) | Medical (N=179) | |
| Dead | 26.9 | 48.9 | 30.4 | 52.0 | Unfavourable |
| Vegetative | 8.5 | 2.1 | 6.2 | 1.7 | |
| Lower Severe Disability | 21.9 | 14.4 | 18.0 | 14.0 | |
| Upper Severe Disability | 15.4 | 8.0 | 13.4 | 3.9 | Favourable |
| Lower Moderate Disability | 10.0 | 10.1 | 10.3 | 7.8 | |
| Upper Moderate Disability | 13.4 | 9.6 | 11.9 | 12.3 | |
| Lower Good Recovery | 2.5 | 3.2 | 7.2 | 3.9 | |
| Upper Good Recovery | 1.5 | 3.7 | 2.6 | 4.5 | |

Table 1 – Primary Outcome Measure Results

Hypothesis generating secondary outcome measures included a lower mortality at 6 months (26.9% vs 48.9%) and 12 months (30.4% vs 50%) in those randomised to surgical decompression. Similarly, this group had more favourable outcomes at 12 months, 45.4% vs 32.4% (P=0.01), with more transitioning into the lower good recovery bracket at this time point, although absolute numbers were small. Quality-of-life data are awaited.

Complications occurred more often in the surgical group than the medical group, 16.3% vs 9.2% (P = 0.03). The higher rate of complications was in large part related to surgical bleeding, post-operative haematoma formation and surgical site infection.

Study critique

The GOS-E has been recommended as a suitable outcome measure in TBI trials.⁸ As significant inter-rater variability can occur, a structured interview is suggested to attain agreement between patient, carer and clinician. In RESCUEicp in the UK, GOS-E questionnaires were mailed to survivors. If no response was obtained, a telephone call was made by a trial member so the questionnaire could be completed with either the patient or carer. This may be a potential source of response bias.

A patient classified as having an upper severe disability can be left alone for at least 8 hours per day but is unable to go shopping or to travel without assistance. This may be

due to physical or cognitive issues. If patients in this category were classified as having an unfavourable outcome, as per usual practice, then at 6 months, the proportions of patients with a favourable outcome on the GOS-E would have been 27.4 vs 26.6% in the surgical and medical groups respectively.

It took 10 years to recruit 408 patients - 39 centres recruited less than 10 patients. This slow rate of recruitment and large proportion of patients excluded may be a source of criticism for some. Conversely it could be argued that decompressive craniectomy, as a third tier, highly invasive treatment, should only be used in a minority of patients and as such, the inclusion and exclusion criteria were proven correct. 37% of the medical group crossed over and eventually underwent decompression. This cross-over would have diluted the actual treatment effect of the surgical intervention. The trial protocol recommended that once randomised, surgery should be delayed no more than 4 to 6 hours. The mean (IQR) time delay to surgery post-randomisation was 2.2 (1.3-5.1) hours, which is comparable with the mean time to surgery in the DECRA trial (2.3 hours).

Mortality was clearly reduced in the surgical group at 6 and 12 months. Did decompression convert non-survivors into survivors left in vegetative or severely disabled state? To what extent is the excess mortality in the medical group due to the high use of barbiturate infusion (87.2%)? Was the lower mortality in the surgical group, in part, due to the low rate of use of barbiturates in the intervention group (9.4%)? Regardless of mortality, the quality of life data which is awaited will perhaps be more meaningful.

Where this sits in the body of evidence

The DECRA trial randomised 155 patients, under the age of 60 and with diffuse, non-penetrating TBI to the early use of decompressive craniectomy (within 72 hours of admission) plus standard care, or standard care alone.⁷ Mean ICP was lower in the surgical group. Unfavourable outcomes on the GOS-E scale at 6 months occurred in 70% of the surgical group compared to 51% of the medical group (OR, 2.21; 95% CI, 1.14 to 4.26; P=0.02). The complication rate was higher in the surgical group (37% vs 17%). Mortality rate at 6 months was similar, 19% vs 18% in the surgical and standard care groups, respectively.

DESTINY was a German multi-centre randomised controlled trial in patients aged 18 to 60 with middle cerebral artery (MCA) infarction. Randomisation was to decompressive craniectomy or standard care alone within 30 hours of stroke onset. The trial was stopped after 32 patients were recruited due to a clear mortality benefit from decompression – 15 of 17 (88%) of surgical patients were alive after 30 days compared with 7 out of 15 (47%) standard care patients. Functional outcome at 6 and 12 months was better in the surgical group, with 47% having a modified Rankin scale score (mRS) of ≤ 3 compared to 27% in the standard care group (P=0.23).⁹



| | DECRA | RESCUEiCP |
|-------------------------|--|---|
| Patients Randomised | 155 | 408 |
| Threshold for inclusion | ICP > 20mm Hg for 15 minutes in any 1 hour period within 72 hours of injury despite 1 st tier therapies | ICP > 25mm Hg for 1 to 12 hours despite stage 1 and 2 therapy |
| Mass Lesions | Surgical Group 4% Medical Group 2% | Surgical Group 18.7% Medical Group 24.2% |
| Surgical Approach | Bifrontotemperoparietal | Frontotemperoparietal Unilateral or Bilateral |
| Upper Severe Disability | Classified as Unfavourable | Classified as Favourable |

Table 2 : A Comparison of DECRA vs RESCUEiCP

The French DECIMAL trial randomised patients < 55 years of age with malignant MCA infarction to decompressive craniectomy or standard care within 36 hours of stroke onset. The primary outcome was of favourable functional outcome at 6 months, as indicated by a mRS ≤ 3. At 6 months 25% of the surgical, vs 5.6% of the standard care group, had a mRS ≤ 3. There was an absolute risk reduction for death of 52.8% in the surgical group (P<0.0001).¹⁰

The randomised controlled HAMLET trial compared decompressive craniectomy with standard care at up to 96 hours after the onset of space-occupying hemispheric infarction. The primary outcome measure was mRS at 1 year, dichotomized to good (mRS 0 to 3) and poor (mRS 4 to 6). This trial was stopped prematurely after 50 patients were evaluable for the primary outcome, with no difference being identified at this time point. Sixty-four patients had been enrolled in total, 32 in each group. Risk of death was lower in the surgical group (ARR 38%; 95% CI 15 to 60; P= 0.002).¹¹

DESTINY II, a prospective, multi-centre, randomised controlled trial, recruited patients with malignant MCA infarction over the age of 60, and compared decompressive craniectomy with standard care within 48 hours of symptom onset. The primary outcome was survival without severe disability at 6 months, indicated by a score of ≤ 4 on the mRS. No survivors in this study had a mRS of 0 to 2. At 6 months, 39% vs 18% survived with a mRS of 3 or 4, in the surgical vs control groups, respectively. Most patients who survived craniectomy in this trial did so with marked disability.¹²

Should we use secondary decompressive craniectomy in TBI?

Maybe. The decision to perform decompressive craniectomy balances the risk of a lower mortality with a higher likelihood of survival with severe disability. The emphasis a patient and family place on survival and disability need to be considered.

References

1. Stocchetti N, Zanier ER. Chronic impact of traumatic brain injury on outcome and quality of life: a narrative review. *Crit Care* 2016;20(1):148.
2. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol* 2013;9(4):231–236.
3. Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. *The Lancet* 2012;380(9847):1088–98.
4. Faul M, Wald MM, Rutland-Brown W, Sullivent EE, Sattin RW. Using a cost-benefit analysis to estimate outcomes of a clinical treatment guideline: testing the Brain Trauma Foundation guidelines for the treatment of severe traumatic brain injury. *J Trauma Acute Care Surg* 2007;63(6):1271–8.
5. Chesnut RM, Temkin N, Carney N, et al. A trial of intra-cranial-pressure monitoring in traumatic brain injury. *N Engl J Med* 2012;367(26):2471–81.
6. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury. *Neurosurgery* 2016 [cited 2016 Oct 13]; Available from: http://www.itls.es/files/Guidelines_for_Management_of_Severe_TBI_4th_Edition.pdf
7. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011;364(16):1493–1502.
8. Weir J, Steyerberg EW, Butcher I, et al. Does the extended Glasgow Outcome Scale add value to the conventional Glasgow Outcome Scale? *J Neurotrauma* 2012;29(1):53–58.
9. Jüttler E, Schwab S, Schmiedek P, et al. Decompressive surgery for the treatment of malignant infarction of the middle cerebral artery (DESTINY) a randomised, controlled trial. *Stroke* 2007;38(9):2518–2525.
10. Vahedi K, Vicaut E, Mateo J, et al. Sequential-design, multi-centre, randomised, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). *Stroke* 2007;38(9):2506–2517.
11. Hofmeijer J, Kappelle LJ, Algra A, et al. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multi-centre, open, randomised trial. *Lancet Neurol* 2009;8(4):326–333.
12. Jüttler E, Unterberg A, Woitzik J, et al. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. *N Engl J Med* 2014;370(12):1091–1100.



HYBERNATUS

Legriel S, Lemiale V, Schenck M, Chelly J, Laurent V, Daviaud F, et al.
Hypothermia for Neuroprotection in Convulsive Status Epilepticus. N Engl J Med 2016;375:2457-67

Introduction

Just over one year ago the International League Against Epilepsy updated the definition of status epilepticus, describing it as *“a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t₁, 5 minutes). It is a condition, which can have long-term consequences (after time point t₂, 30 minutes), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.”*¹ This prolonged state of uncontrolled cortical activity manifesting as seizures is the second most frequent neurological emergency after stroke.² Despite this, status epilepticus is relatively uncommon, being responsible for just 0.07% of all American hospital admissions from 1979 to 2010.³ Its incidence has risen over this time period, from 3.5/100,000 to 12.5/100,000 of the population.³ 85% require mechanical ventilation and outcomes can be poor.⁴ For status epilepticus, 90 day mortality is approximately 20%;⁴ for refractory status epilepticus this reaches 40%.² Over two-fifths suffer severe functional impairments. The most common causes of status epilepticus are withdrawal of anti-convulsant drugs and stroke.⁴

Specific treatment aims to stop seizures as soon as possible, before the onset of neuronal injury or death, and consists of an escalating range of anti-convulsants, up to the induction of general anaesthesia. Mortality has largely remained unchanged, despite improving critical care outcomes in general.³

Hypothermia has emerged as a potential neuroprotective intervention, offering anti-convulsant, anti-inflammatory, anti-apoptotic, anti-cytotoxic, and anti-excitatory effects, as well as beneficial actions on blood brain barrier permeability, lessening cerebral oedema formation.⁵ Hypothermia has been successfully used for many years in neonatal hypoxic-ischaemic encephalopathy,⁶ and more recently has been investigated in a range of conditions including post cardiac arrest,⁷ bacterial meningitis,⁸ subarachnoid haemorrhage,⁹ stroke^{10,11} and myocardial infarction.¹²

Study synopsis

The investigator-initiated HYBERNATUS (Hypothermia for Brain Enhancement Recovery by Neuroprotective and Anti-convulsant Action after Convulsive Status Epilepticus) trial was a parallel group, assessor-blinded, randomised controlled trial undertaken in 11 French ICUs between 2011 and 2015. It compared induced hypothermia (32 to 34 °C) plus standard care with standard care alone, in critically ill patients suffering from



convulsive status epilepticus and requiring mechanical ventilation.

Inclusion criteria were age over 18 years, convulsive status epilepticus (5 minutes or more of either continuous seizure activity or two or more seizures without return to baseline) within the previous 8 hours plus the receipt of mechanical ventilation. Exclusion criteria were a return to their premorbid level of consciousness, an inability to receive therapeutic hypothermia (such as the need for emergency surgery or bacterial meningitis), post anoxic status epilepticus, a do-not-resuscitate order or an expectation for imminent death. Patients underwent web-based computer-generated permuted-block randomisation in a 1:1 fashion, stratified for centre, age (younger or older than 65 years of age) and seizure duration (less than or greater than 60 minutes). Surrogate approved consent was obtained pre-randomisation, with delayed written participant consent sought after recovery from illness.

Patients with seizures were managed in line with current French guidelines, receiving an initial dose of a benzodiazepine, followed by the addition of a second non-benzodiazepine anti-convulsant if seizures had not terminated. At 60 minutes, if seizures were still not controlled, propofol boluses were commenced, followed by a propofol infusion. An additional anaesthetic agent (midazolam or thiopentone) could also be added if the patient remained in refractory status epilepticus. Status epilepticus was to be controlled within 60 minutes of randomisation and prior to the initiation of cooling.

Temperature was measured with an oesophageal thermometer. The target range of 32 to 34 °C was induced with ice-cold intravenous fluids at 4 °C and maintained with ice-packs at the groin and neck plus cold air convection. This temperature was to be achieved as soon as possible post randomisation and maintained for 24 hours. The hypothermia group received protocolised sedation, with propofol plus neuromuscular blockade, while the control group received protocolised propofol sedation only if deemed necessary by the treating physician. Both groups received continuous EEG monitoring, with seizures treated with propofol, consisting of boluses and subsequent infusion, aiming for burst-suppression for 24 hours.

The primary outcome was survival with a Glasgow Outcome Scale (GOS) score of 5, independently adjudicated at day 90. The GOS ranges from 1 (death) to 5 (none or minimal neurological deficit). Four groups of secondary outcomes were assessed: (1) mortality - in-ICU, in-hospital and at day 90; (2) seizure activity - progression to EEG-confirmed status epilepticus between 6 and 12 hours post randomisation, refractory status epilepticus at day 1 despite administration of at least 2 anti-epileptic drugs, super-refractory status epilepticus at day 2 despite anaesthetic agents, total seizure duration; (3) lengths-of-stay - ICU and hospital; and (4) impairment at day 90.

Based on prior data, 135 patients were required per group to identify a 20% absolute



difference in the percentage of patients achieving a GOS score of 5 at day 90 (hypothermia group 60% vs control group 40%) with a power of 90% at the 5% significance level. One planned interim analysis was undertaken. Analyses were performed as per a pre-published statistical plan, on an intention-to-treat basis, and included sensitivity analyses for missing outcomes.

803 patients were screened, with 533 excluded, mainly for a failure to meet inclusion criteria. In total, 270 patients were randomised: 138 patients to hypothermia, 130 to standard care and 2 patients were randomised but withdrew consent. One patient from each group had further status epilepticus and both were enrolled again. Groups were largely similar at baseline. The median patient age was 57 and 65% were male. 65% had an out-of-hospital onset of seizure, largely bystander witnessed, with the majority being generalised seizures (>85%). 51% of the hypothermia group and 46% of the control group were epileptic. The type and timing of first anti-epileptic drug was the same in both groups – 83% received a benzodiazepine at a median time of 40 minutes after onset of seizure. A median of 2 anti-epileptic drugs were required to control seizures, which occurred at a median of 80 minutes (IQR 40 to 210). 23 and 27% of the hypothermia and control groups, respectively, had refractory status epilepticus at randomisation. Temperatures were similar at 37.0 °C.

The intervention was adequately delivered with good separation in temperatures between groups. 98% of the hypothermia group reached the targeted temperature range within a median of 5.2 hours (IQR 3.5 to 7.1). The control group stayed at approximately 37 °C. The amount of cold intravenous fluid administered to achieve hypothermia was not stated.

There was no statistical difference in the primary outcome of a GOS score of 5 (hypothermia group 49% vs control group 43%; odds ratio with hypothermia 1.22; 95% CI, 0.75 to 1.99; P=0.43). Sensitivity analyses yielded similar results. Secondary endpoints were also largely similar between groups, with the exception of less patients in the hypothermia group progressing to EEG-confirmed status epilepticus (OR, 0.40; 95% CI, 0.20 to 0.79; P=0.009). There were no significant differences in refractory status epilepticus at day 1 (hypothermia vs control, 31% vs 38%; OR 0.68, 95% CI 0.40 to 1.15; P=0.15) or super-refractory status epilepticus at day 2 (17% vs 23%; OR 0.64, 95% CI 0.34 to 1.19; P=0.16). There were no significant differences in mortality at any timepoint (hypothermia vs control; icu: 9% vs 12%; in-hospital: 12% vs 15%; day 90: 18% vs 20%). No difference in functional impairment at day 90 was seen. In predefined subgroup analyses, heterogeneity of effect was seen with age. Patients younger than 65 years of age treated with hypothermia were more likely to achieve a GOS score of 5 (OR, 1.75; 95% CI, 0.98 to 3.16), while those over 65 were less likely to achieve this outcome (OR, 0.49; 95% CI, 0.19 to 1.25). More patients in the hypothermia group suffered an adverse event (85% vs 77%).



Study critique

Continuing on a popular theme of inducing hypothermia for cerebral protection, the HYBERNATUS study sought to improve outcomes from convulsive status epilepticus. The logistics of the trial appear sound, including pre-publication of the trial protocol, multi-centre recruitment, rationale inclusion and exclusion criteria, robust randomisation and allocation, achievement of similar groups at baseline, use of national seizure guidelines for anti-convulsant therapy, adequate inter-group temperature separation and independent blinded outcome assessment.

At face value, it appears induced therapeutic hypothermia offers little benefit in the management of convulsive status epilepticus. Some mostly non-significant differences in seizure durations and progression were seen in favour of hypothermia, but these failed to translate into anything longstanding. However, the reported results raise questions regarding the seizure management of each group. For instance, it is somewhat surprising, that for a seizure trial, doses of anti-epileptics aren't described. The types of drugs used are reported, and are largely similar between groups, but no doses are given. The closest we can derive from the published results is that 100% of the hypothermia group received propofol, which was required by the protocol, versus 94% of the control group. As anti-convulsants are not benign drugs, this is important information to know. For instance, benzodiazepine use is associated with both the development of, and a worse outcome from, delirium. Did those treated with hypothermia need a greater dose of anti-convulsants, risking complications from this therapy and thus reducing any possible between group difference for the primary outcome, or perhaps did they need less, and the signal seen could be due to a reduction in anaesthetic agent use?

While continuous EEG monitoring was used, the respective depths of sedation between the groups over the duration of their period of mechanical ventilation is not clarified. Again, deeper sedation is associated with poorer outcomes, so this would be interesting to know.

The total numbers progressing to EEG-confirmed status epilepticus is low, with just 15 and 29, in the hypothermia and control groups, respectively. Perhaps a study recruiting more patients still in a seizure state would be more likely to identify a therapeutic effect.

Anti-convulsants are one potential confounder. The cold fluid administered to achieve the target temperature range is another and is sparsely described. Which fluids were used, at what volume, rate and to what effect on total fluid balance?

Where this sits in the body of evidence

The open-label EURO THERM 3235 randomised controlled trial compared standard care plus induced hypothermia of 32 to 35 °C with standard care alone in 387 patients from



18 countries with traumatic brain injury-associated intra-cranial hypertension.¹³ Hypothermia was used as a stage 2 measure, before osmotherapy in the interventional group, and was induced with 20 to 30 ml/kg of ice cold saline, maintained with the usual technique of each centre for at least 48 hours followed by gradual rewarming at 0.25°C per hour until core temperature was $\geq 36^\circ\text{C}$. Despite achievement of hypothermia in the interventional group, with an inter-group separation of over 2°C, and better intra-cranial pressure control, hypothermia was associated with worse neurological outcomes (adjusted common OR, 1.53; 95% CI, 1.02 to 2.30; P=0.04) necessitating early termination of the trial.

The French multi-centre open-label HPOTOTAM trial compared standard care plus induced hypothermia of 32°C to 34°C with standard care in 98 comatose adults with early community-acquired bacterial meningitis.⁸ Hypothermia was induced with 1500 to 2000 ml cold saline, maintained for 48 hours with each centre's usual temperature management technique and followed by passive rewarming. 77% of patients had pneumococcal meningitis. Despite a clear difference in group temperatures (mean/IQR) at 24 hours (33.3/0.9°C vs 37.0/0.9°C), the trial was stopped early for harm, with an unadjusted mortality excess (51% vs 31%, RR, 1.99; 95% CI, 1.05 to 3.77; P=0.04). This lost significance after adjusting for several baseline variables, but the probability of achieving a significant benefit was very low. No signal of benefit was identified.

The Targeted Temperature Management (TTM) trial by Nielsen and colleagues was a large international multi-centre, open-label, randomised controlled trial comparing temperature management of 33°C with 36°C in 950 unconscious adults after out-of-hospital cardiac arrest of presumed cardiac origin.⁷ The assigned temperature was achieved as rapidly as possible by whatever temperature management technique chosen by each centre and maintained for 28 hours. Rewarming then occurred by 0.5°C per hour until a core temperature of 37°C was reached and maintained until 36 hours. Temperature was kept $< 37.5^\circ\text{C}$ in still comatose patients until 72 hours. Both groups achieved the assigned temperatures. There were no differences in either the primary outcome of end of trial mortality (33°C group 50% versus 48% in the 36°C group; HR with 33°C, 1.06; 95% CI, 0.89 to 1.28; P=0.51), or any secondary outcomes.

The ICTuS group of trials are a series of investigations examining whether combined thrombolysis (intravenous r-tPA) with a hypothermia/anti-shivering regimen is superior to thrombolysis alone for the treatment of acute (< 3 hours) ischemic stroke.¹¹ Hypothermia was induced with a rapid infusion of 2000 ml of saline at 4°C and maintained with an intravascular cooling device for 24 hours, followed by gradual rewarming over 12 hours. Interventions to manage shivering included pethidine, buspirone, and skin warming. The study was stopped early after 120 of a planned 400 patients were recruited, due to funding expiration and the approval of intra-arterial neurothrombectomy. There was no signal of benefit with hypothermia, either for the



primary measure of a favourable outcome (90-day modified Rankin Score of 0 or 1; hypothermia group 33% vs normothermia group 38%; OR, 0.81; 95% CI, 0.36 to 1.85) or secondary measures, including mortality (15.9% vs 8.8%, respectively; OR, 1.95; 95% CI 0.56 to 7.79).

COOLIST was another stroke hypothermia trial very recently published this winter in *Stroke*. This was a multi-centre, open label, phase II randomised controlled trial, evaluating tolerability to surface cooling to 34.0°C, 34.5°C, or 35.0°C in awake patients with acute (<4.5 hours) ischemic stroke and an National Institutes of Health Stroke Scale score of ≥ 6 .¹⁰ This trial was also stopped early, after just 22 patients were enrolled. While cooling to 35°C was tolerable, temperatures colder than this were not tolerated. A further trial examining induced hypothermia in stroke is currently underway (EuroHYP-1, <http://www.eurohyp1.eu/>).

Induced hypothermia has also been unsuccessfully investigated in subarachnoid haemorrhage. The IHAST (intra-operative Hypothermia for Aneurysm Surgery) Trial compared intra-operative hypothermia at 33°C, achieved with surface cooling, with normothermia (36.5°C) in 1001 patients with good grade subarachnoid haemorrhage.¹⁴ There were no significant outcome differences between the groups. Hypothermia has also been tested in acute myocardial infarction. Several small trials have reported reduced infarction size, but no effect on more meaningful patient centred outcomes.¹²

Should we induce hypothermia in mechanically ventilated patients with convulsive status epilepticus?

No, this trial does not support the use of induced hypothermia in mechanically ventilated patients with status epilepticus.

References

1. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015;56(10):1515–23.
2. Rossetti AO, Lowenstein DH. Management of refractory status epilepticus in adults: Still more questions than answers. *Lancet Neurol* 2011;10(10):922–30.
3. Dham BS, Hunter K, Rincon F. The Epidemiology of Status Epilepticus in the United States. *Neurocrit Care* 2014;20(3):476–83.
4. Legriél S, Azoulay E, Resche-Rigon M, et al. Functional outcome after convulsive status epilepticus. *Crit Care Med* 2010;38(12):2295–303.
5. Gibson A, Andrews PJ. Therapeutic hypothermia, still “too cool to be true?” *F1000Prime Rep* 2013;5:26–9.
6. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-Body Hypothermia for Neonates with Hypoxic–Ischemic Encephalopathy. *N Engl J Med* 2005;353(15):1574–84.
7. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest. *N Engl J Med* 2013;369(23):2197–206.
8. Mourvillier B, Tubach F, Van de Beek D, et al. Induced hypothermia in severe bacterial meningitis: a randomised clinical trial. *JAMA* 2013;310(20):2174–83.
9. Komotar RJ, Jones JE, Connolly JR ES. Intra-operative Hypothermia for Aneurysm Surgery Trial (IHAST). *Neurosurgery* 2005;56(3):N9–10.
10. Geurts M, Petersson J, Brizzi M, et al. COOLIST (Cooling for Ischemic Stroke Trial). *Stroke* 2016; epublished November 17th.
11. Lyden P, Hemmen T, Grotta J, et al. Results of the ICTuS 2 Trial (Intravascular Cooling in the Treatment of Stroke 2). *Stroke* 2016;47(12):2888.
12. Villablanca PA, Rao G, Briceno DF, et al. Therapeutic hypothermia in ST elevation myocardial infarction: a systematic review and meta-analysis of randomised control trials. *Heart* 2016;102(9):712–9.
13. Andrews PJD, Sinclair HL, Rodriguez A, et al. Hypothermia for intra-cranial Hypertension after Traumatic Brain Injury. *N Engl J Med* 2015;373(25):2403–12.
14. Todd MM, Hindman BJ, Clarke WR, Torner JC. Mild intra-operative Hypothermia during Surgery for intra-cranial Aneurysm. *N Engl J Med* 2005;352(2):135–45.



Dexmedetomidine for Delirium in Non-Cardiac Surgery

Su X, Meng Z, Wu X, Cui F, Li H, Wang D et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *The Lancet* 2016;388(15004):1854-1856

Introduction

Delirium in critically ill patients has been extensively studied over the past 15 years, following recognition that it is common, occurring in up to 82% of mechanically ventilated patients, and has implications beyond the distress caused to patients, relatives and staff. It is an independent predictor of long-term mortality and cognitive impairment,^{1,2} and can be seen as a form of acute organ dysfunction akin to renal or cardiac failure. To date, its multi-factorial basis has prevented the identification of a specific biomarker or consistent single neurotransmitter abnormality.³

Although there have been successful trials of non-pharmacological interventions aimed at preventing the onset of delirium, pharmacological studies have provided mixed results.³ Dexmedetomidine is an α_2 adrenoreceptor agonist with sedative, anxiolytic and analgesic properties which has less respiratory depressive effects than other sedatives.⁴ When given by infusion in ICU it is associated with a lower incidence of delirium than propofol or midazolam;⁵ however, its ability to preventing the onset of delirium post-operatively is less established.

Study synopsis

This randomised, placebo-controlled study investigated whether prophylactic dexmedetomidine prevents delirium in ICU patients over 65 years of age following elective non-cardiac surgery under general anaesthesia (GA). It was conducted in two University Hospital ICUs in Beijing, China, between 2011 and 2013. Potential participants were screened post-operatively on arrival to ICU if admitted before 8pm. Consent was obtained from the patient if orientated or otherwise from the next of kin or legal representative. Randomisation was computerised and in a 1:1 ratio.

Dexmedetomidine (0.1 $\mu\text{g}/\text{kg}/\text{hr}$) or matching saline placebo was given as a continuous infusion. It was started at ICU admission in non-intubated patients and after sedative infusions (propofol or midazolam) were titrated to a Richmond Agitation Sedation Scale (RASS) of -2 or higher in those intubated. It was continued until 8am on the first day after surgery. Analgesia was given as necessary. There were set criteria for extubation based on adequate respiration, conscious level and haemodynamic stability.

ICU standard operating procedures included measures aimed at minimising delirium (early mobilisation, reorientation, visual aids, hydration and sleep-promotion). Delirium



was initially managed non-pharmacologically and haloperidol given if this failed and RASS was $\geq +3$ (severe agitation). Open-label dexmedetomidine was not permitted. Anaesthetists, nurses and those performing delirium assessments were blinded to the intervention.

The primary endpoint was the incidence of delirium in the first post-operative week. Secondary endpoints included time to extubation, ICU and hospital lengths of stay, pain scores, sleep quality, medical complications and 30-day mortality. Cardiovascular and respiratory adverse events were defined; bradycardia as a heart rate <55 bpm and tachycardia >100 bpm; hypotension as systolic blood pressure <95 mm Hg and hypertension as >160 mm Hg. If these limits were close to baseline values then a change of 20% was considered significant instead. Hypoxaemia was defined as a $SpO_2 < 90\%$ or 5% less than baseline.

Delirium was assessed with the ICU Confusion Assessment Method (CAM-ICU), initially at 24 hours post-op and twice daily thereafter. If present, delirium was categorised as hyperactive, hypoactive or mixed depending on the predominant RASS score. A sample size of 700 patients would have 80% power to detect a 30% decrease in the incidence of delirium, from an anticipated baseline of 28%,⁶ at the 5% significance level with an anticipated 6% loss to follow-up. Analyses were by intention-to-treat but also per-protocol for some endpoints. The Braun Anaesthesia Research Fund and Wu Jieping Medical Foundation funded the study.

2,016 patients were screened for eligibility and 700 randomised. 1,181 met preset exclusion criteria {636 <65 years old, 94 non-surgical, 183 non-general anaesthesia, and 268 other (neurosurgical operation, pre-operative coma, dialysis, cardiac failure or Parkinsonism)}; consent was not obtainable in 135. There were 350 patients in each group; all were included in the final analysis. Baseline characteristics were similar. Mean age was 74, 60% were male. The majority of operations were intra-abdominal or intra-thoracic (85%); with 75% for malignancy. Placebo group patients were slightly more likely to receive midazolam intra-operatively (173 vs 153) and had a longer duration of surgery (238 vs 219 minutes). 191 (54.6%) patients in each group were intubated on admission to ICU; mean APACHE II scores (10.6 / 10.2) and study drug infusion duration (14.6 / 15.0 hours) were similar. post-operatively, the majority received intravenous sufentanil patient-controlled analgesia (74%) or epidural analgesia (16%). In the placebo / dexmedetomidine groups the use in the first 7 days of propofol (51% / 51%); morphine (29% / 28%) and midazolam (10% / 7%) was similar; a higher total dose of propofol was required in the placebo group (median 275 vs 250 mg). In the first 7 days 2 patients died and 143 were discharged from hospital.

The incidence of delirium was significantly higher in the placebo group (primary outcome, 23% vs 9%; OR, 0.35; 95% CI, 0.22 to 0.54; $p < 0.0001$; NNT=7.4); with similar

positive results in the per-protocol analysis, in all motor subtypes of delirium and whether intubated or not on ICU admission. The placebo group also had a prolonged median time to extubation (6.9 hrs vs 4.6 hrs, HR 1.25; 95% CI, 1.02 to 1.53; P=0.031) and more medical complications (21% vs 15%; OR, 0.66; 95% CI, 0.45 to 0.98; P=0.39). There were no significant differences in hospital length of stay or mortality; there was a clinically insignificant longer median ICU length of stay with placebo of 0.6 hours (P=0.027).

The dexmedetomidine group had a small but significant reduction of ≤ 1 point in the median pain scores measured by a 10-point numerical rating scale (NRS) (P<0.001 for most time points); and a statistically significant improvement in subjective sleep quality scores. Tachycardia, hypertension and hypoxaemia were significantly more common in the placebo group, and bradycardia and hypotension more frequent in the dexmedetomidine group (non-significant); overall 23% of patients in the placebo and 16% in the dexmedetomidine group required medical intervention for deranged physiology. Modification of the study drug infusion was required in 9% vs 5% of patients in the dexmedetomidine and placebo groups, respectively. RASS scores were similar between groups; only 3 patients (0.4%) received haloperidol.

Study critique

This is a significant study with an intriguing result. It appeared to be well conducted, with a moderately large sample size, few protocol violations and the inclusion of all patients in the primary outcome analysis. Both the patient and those assessing for outcomes were blinded as to the treatment allocation. The study population was relatively homogenous and well defined. The size of the reduction in incidence of delirium seen (absolute risk reduction of 13%, relative risk reduction of 61%) is clinically as well as statistically significant. Previous ICU prevention studies have been less successful;⁷ it is therefore important to consider if this result is likely to be replicable. In this regard, there are potential issues relating to the trial methodology, application of the protocol and the clinical impact of the intervention.

A major issue is that although the study population was undergoing elective surgery, the patients were only screened and recruited when admitted to the ICU post-operatively. At this stage 55% were intubated and sedated, and the remaining patients had all recently emerged from GA. This probably explains why consent by a family member was required in 58% of patients.⁸ Whilst surrogate consent is used extensively in ICU trials, this is usually in the setting of acute critical illness where there is no prior opportunity for individuals to be fully informed. It is difficult to imagine consenting patients pre-operatively would not have been ethically preferable. The trial did have institutional ethical approval.

Patients were not screened for delirium or cognitive impairment at enrolment, which



makes it impossible to state with certainty that the difference seen in delirium rates subsequently did not at least partially reflect a random difference present at baseline. The trialists state this was to avoid diagnosing emergence delirium which they contend is a separate entity, but this is controversial.⁹ As it would be unfeasible to complete the CAM-ICU assessment due to deep sedation in many on arrival this again could have been performed pre-operatively. It is also interesting that midazolam was a permitted sedating agent as it has been previously implicated in causing delirium.¹⁰

The incidence of delirium was approximately double in those intubated on admission (20% vs 11%), which may have been related to sedative medications or a reflection of an increased severity of illness. There was an exact balance of the number of patients intubated / extubated on admission (191 / 159) in each group. Overall randomisation was in a 1:1 ratio, but it was not noted to be stratified by intubation status.

Although dexmedetomidine infusion was given at a lower dose (0.1 µg/kg/hr) than recommended for ICU sedation (0.2 - 1.7 µg/kg/hr) there was evidence of the α₂ agonist pharmacological effects of the drug with a propofol-sparing and analgesic effect noted and a lower incidence of tachycardia or hypertension. It is possible bedside staff would be able to recognise these effects on an individual patient basis, potentially unblinding the group allocation and risking bias. All infusions were stopped at 8am to enable residual drug clearance before a potential afternoon ward discharge. This led to a potential under-dosing of some patients that would be consistent with the non-significant effect on delirium rates seen with the lowest quartile of drug duration. The incidence of non-delirium complications was lower with dexmedetomidine but these were diverse and difficult to firmly attribute to the study drug. Additionally, it appears different total figures for complications are presented in the manuscript (73 placebo, 52 dexmedetomidine) and the appendix (93 placebo, 70 dexmedetomidine.)

The CAM-ICU is an adaption of the Confusion Assessment Method (CAM), allowing its use in non-verbalising mechanically ventilated patients. A positive test requires documentation of a fluctuating or acutely changed mental status alongside recognition of inattention, with either disorganised thinking or an altered level of consciousness. It has been extensively evaluated in differing ICU populations since its original description, including in Chinese patients.¹¹ Although widely used, several of its components are vulnerable to confounding by the ongoing use of sedatives, and it may under-diagnose delirium when compared to the CAM in those able to verbalise. For these reasons evidence of clinical benefit beyond the incidence of CAM-ICU diagnosed delirium is desirable in intervention studies. Although the avoidance of delirium may be an important patient-centred outcome it did not translate in this study into a reduction in hospital length of stay.

In summary this trial has shown a potential beneficial effect of low-dose



dexmedetomidine in post-operative elderly patients. Further studies replicating these results are awaited.

Where this sits in the body of evidence

In 2001 Ely and colleagues prospectively tested the recently developed CAM-ICU tool in 111 consecutive mechanically ventilated patients.¹² When compared to assessment by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSMD) delirium criteria, the CAM ICU performed by 2 study nurses had a sensitivity, specificity and inter-rater reliability of >90% for the diagnosis of delirium. In 2013 Wang et al validated a simplified Chinese version of the CAM-ICU in 126 patients (22 ventilated) and noted a similar sensitivity, specificity and reliability.¹¹

In 2007 Pandharipande and colleagues randomised 106 mechanically ventilated ICU patients to sedation with dexmedetomidine or lorazepam for up to 120 hours, titrated to RASS.¹⁵ The dexmedetomidine group had more days without CAM-ICU diagnosed delirium or coma (7.0 vs 3.0 days, $P=0.01$) and were within one point of target RASS score for a higher proportion of time (80% vs 67%, $P=0.04$).

Reade and colleagues completed an open-label pilot study randomising 20 ventilated patients with agitated delirium to an infusion of haloperidol (0.5 to 2mg/hour) or dexmedetomidine (0.2 to 0.7 $\mu\text{g}/\text{kg}/\text{hr}$).¹⁸ Those receiving dexmedetomidine were extubated faster and had a decreased length of ICU stay (1.5 vs 6.5 days, $P=0.004$).

Riker et al randomised 375 ICU patients to dexmedetomidine- or midazolam- based sedation.⁶ Time spent within target RASS range was similar (primary outcome). The dexmedetomidine group had less delirium (54% vs 76.6%; difference, 22.6%; 95% CI, 14% to 33%; $P=0.001$) and shorter median time to extubation (3.7 vs 5.6 days, 95% CI, 4.6 to 5.9; $P=0.01$) but more bradycardia (42% vs 18.9%; $P=0.001$).

In 2012 Jakob reported in one publication the results of two non-inferiority studies comparing dexmedetomidine with midazolam (MIDEX trial, 44 European centres) and propofol (PRODEX, 33 European centres) for prolonged ICU sedation. Centres entered the trial using their usual sedative agent as control.¹³ Dexmedetomidine met non-inferiority criteria in both studies, and reduced median duration of mechanical ventilation in the MIDEX arm (123 vs 164 hours, $P=0.03$), but with more reported adverse effects. The incidence of delirium, as diagnosed by CAM-ICU at 48 hours, did not differ in either study.

The DahLia trial, published in early 2016, randomised 71 ICU patients with agitated delirium to dexmedetomidine (0.5 to 1.5 $\mu\text{g}/\text{kg}/\text{hr}$) or placebo alongside usual care (96% were receiving propofol).¹⁴ Median ventilator-free hours (primary outcome) were increased in the dexmedetomidine group (145 vs 128 hours; $P=0.01$). Delirium also



resolved more quickly (23 vs 40 hours; $P=0.01$). Adverse events were rare. Recruitment was halted early after the sponsor declined to extend funding.

Devlin et al randomised 36 delirious ICU patients to quetiapine (50mg to 200mg 12-hourly) or placebo.¹⁶ Patients treated with quetiapine had a shorter duration of delirium (36 vs 120 hrs; $P=0.006$), similar rates of QTc prolongation, but more somnolence. ICU length of stay and mortality was similar.

In 2010 van Eijk et al randomised 104 of a planned 440 delirious ICU patients to rivastigmine (1.5 to 6mg twice daily) or placebo as an adjunct to open-label haloperidol.¹⁷ The study was stopped by the data safety and monitoring board after a planned interim analysis showed a non-significant increase in mortality (22% vs 8%, $P=0.07$) and duration of delirium with rivastigmine (5.0 vs 3.0 days, $P=0.06$).

Should we implement this into our practice?

No- we should await further study of the safety and efficacy of using low-dose dexmedetomidine to prevent delirium

References

1. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004;291(14):1753–62.
2. van den Boogaard M, Schoonhoven L, Evers AWM, van der Hoeven JG, van Achterberg T, Pickkers P. Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. *Crit Care Med* 2012;40(1):112–8.
3. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *Lancet Lond Engl* 2014;383(9920):911–22.
4. Su X, Meng Z-T, Wu X-H, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *The Lancet* 2016;388(10054):1893–902.
5. Xia Z-Q, Chen S-Q, Yao X, Xie C-B, Wen S-H, Liu K-X. Clinical benefits of dexmedetomidine versus propofol in adult intensive care unit patients: a meta-analysis of randomised clinical trials. *J Surg Res* 2013;185(2):833–43.
6. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomised trial. *JAMA* 2009;301(5):489–99.
7. Page VJ, Ely EW, Gates S, et al. Effect of intravenous haloperidol on the duration of



- delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2013;1(7):515–23.
8. Kronzer VL, Avidan MS. Preventing post-operative delirium: all that glitters is not gold. *The Lancet* 2016;388(10054):1854–6.
 9. Sharma PT, Sieber FE, Zakriya KJ, et al. Recovery room delirium predicts post-operative delirium after hip-fracture repair. *Anesth Analg* 2005;101(4):1215–20.
 10. Fraser GL, Devlin JW, Worby CP, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomised trials. *Crit Care Med* 2013;41(9 Suppl 1):S30–8.
 11. Wang C, Wu Y, Yue P, et al. Delirium assessment using Confusion Assessment Method for the Intensive Care Unit in Chinese critically ill patients. *J Crit Care* 2013;28(3):223–9.
 12. Ely EW, Inouye SK, Bernard GR, et al. Delirium in Mechanically Ventilated Patients: Validity and Reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *JAMA* 2001;286(21):2703.
 13. Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomised controlled trials. *JAMA* 2012;307(11):1151–60.
 14. Reade MC, Eastwood GM, Bellomo R, et al. Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium: A randomised Clinical Trial. *JAMA* 2016;315(14):1460–8.
 15. Pandharipande PP, Pun BT, Herr DL, et al. Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients: The MENDS randomised Controlled Trial. *JAMA* 2007;298(22):2644.
 16. Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multi-centre, randomised, double-blind, placebo-controlled pilot study*. *Crit Care Med* 2010;38(2):419–27.
 17. van Eijk MMJ, Roes KCB, Honing MLH, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multi-centre, double-blind, placebo-controlled randomised trial. *Lancet Lond Engl* 2010;376(9755):1829–37.
 18. Reade MC, O’Sullivan K, Bates S, Goldsmith D, Ainslie WR, Bellomo R. Dexmedetomidine vs haloperidol in delirious, agitated, intubated patients: a randomised open-label trial. *Crit Care* 2009;13(3):R75.



Light Therapy for Delirium

Simons K, Laheij R, van den Boogaard M, Moviat M, Paling A, Polderman F, et al. Dynamic light application therapy to reduce the incidence and duration of delirium in intensive-care patients: a randomised controlled trial. *Lancet Respir Med* 2016;4:194–202

A discrete pathophysiological mechanism for delirium remains elusive, with current evidence suggesting that individual cases are caused by the interaction of elements drawn from sets of biological factors that may include a range of neurotransmitters, cytokines, hormones, drugs, and disorders of electrolytes or physiology. These unique combinations lead to the disruption of neuronal networks and the clinical manifestations of delirium: fluctuating disorders of consciousness, attention and cognition. There is therefore a myriad of identified factors which can be causally linked to the condition, but pharmacologically targeting an individual one is often unsurprisingly unsuccessful.¹

Non-pharmacological methods have the potential to act generically and lessen the impact of delirium whatever its cause. They are the mainstay of delirium prevention in the non-ICU setting, with good evidence for a multicomponent strategy encompassing reorientation, mobilisation, sleep promotion, hydration and provision of hearing and visual aids.² The ICU environment potentially contributes negatively to all of these factors, with sleep disturbance almost universal due to noise, sedative drugs and ambient light. There have been attempts to modify this with the use of nocturnal earplugs with some success.^{1,3} Bright-light therapy aims to restore circadian rhythms and promote sleep, potentially beneficially impacting on the significant burden of ICU-acquired delirium. This was the focus of this study.

Study synopsis

This was a single-centre, unblinded, randomised controlled trial performed in a Dutch teaching hospital ICU. Ethical approval and individual or surrogate consent were obtained. Eligible patients were over 18 years old and expected to be in ICU for over 24 hours. Those with anticipated imminent death or contra-indication to completing delirium assessments were excluded. Randomisation was computerised and in a 1:1 ratio.

The intervention was an adjustable bright lighting system (supplied by Philips Lighting, Eindhoven) installed into each ICU room, controlled centrally by the investigators and with a peak intensity of 1700 lux, giving 800-1000 lux bluish-white (4300 K) light at patient level. Photometers measured illuminance every 15 minutes. It was applied with increasing intensity from 0700 h to peak at 0900 h and maintained until 1130 h; this was repeated from 1330 h until 1700 h. In-between these spells and afterwards until 2230 h a lower light level of 300 lux, 3000 K colour temperature was applied as a rest period;



the lights were switched off at 2230. The control group had lights at 300 lux, 3000 K; controlled within the room. Thirty minutes of extra light (1000 lux) was available from within the room for procedures at any time in both groups.

Delirium risk was predicted on admission to ICU with the PRE-DELIRIC model (developed by the authors); delirium screening was performed three times daily by bedside staff using the Confusion Assessment Method for the ICU (CAM-ICU). The primary outcome was the cumulative incidence (at least one positive CAM-ICU screening) of ICU-acquired delirium. Delirium assessments continued after ICU discharge, utilising assessment by the Delirium Outcome Score (DOS), geriatrician consultation or use of haloperidol. Secondary outcomes included the number of delirium-free days in 28 days, duration of mechanical ventilation and length of stay (LOS) within ICU and the hospital. A subgroup of 20 patients had multiple urine samples taken for analysis of cortisol and a melatonin metabolite in order to examine any effects on circadian rhythms.

The planned recruitment of 1000 patients was calculated to have 90% power (two-sided α 0.05) to detect a 10% absolute reduction in the anticipated 40% delirium incidence in the control group. Analyses were by intention-to-treat, but per-protocol analysis was also conducted (those who were exposed to the correct light therapy for >80% of their ICU stay) and various subgroups were prospectively defined for exploratory analyses.

Recruitment was halted for futility after an interim analysis in September 2013. At this stage 1374 eligible patients had been identified, 640 were excluded (400 expected ICU LOS <24 h, 167 refused, 29 did not speak Dutch, 19 were not expected to survive, 16 had hearing or visual impairment, 9 other). Of the 734 randomised (the intention-to-treat population), 361 were assigned to the Dynamic Light Application (DLA) intervention and 373 to control. A further 20 were excluded from the per-protocol analysis; 18 because their actual LOS was <24 h and two had been randomised in error. Baseline characteristics were similar: in the DLA / control groups mean age was 66 / 64 years; mean APACHE II score was 23 / 22; 32% / 33% had sepsis and 21% / 21% acute kidney injury. Cognitive impairment was present in 10% / 7%; alcoholism in 7% / 7% and 95% in each group were admitted to rooms with windows and natural daylight. The differences in age and a medical diagnosis (73% / 65%) were statistically significant.

Adherence to the lighting protocol was 100%. Photometer data (missing in 23 patients) confirmed a significant difference in mean cumulative daylight lighting levels (mean \pm SD in DLA group 5366 \pm 1590 lux vs 2793 \pm 1419 lux in control; $P < 0.0001$). There was more seasonal variation in daytime light levels in the control group. No adverse events were reported.

There was no difference in the cumulative incidence of delirium (primary outcome) between the DLA and control groups (38% vs 33%; OR, 1.24; 95% CI, 0.92 to 1.68;

P=0.16. There was also no difference in delirium free days (26 vs 27 days; P=0.24), length of stay or mortality in ICU or hospital (hospital LOS 15 vs 16 days; P=0.57; hospital mortality 18% vs 19%; P=0.78). There was no evidence of a reduced duration or delayed onset of delirium with DLA.

Delirium occurrence was associated with older age, higher APACHE II score and a history of cognitive disturbance, alcoholism or smoking. Patients with delirium were more likely to be intubated, receive prolonged mechanical ventilation, be on sedative infusions and at higher doses (all significant statistically apart from cumulative midazolam dose). ICU and hospital LOS were longer in those with delirium, mortality did not differ (median hospital LOS delirium 23 days vs 12 if not, P<0.0001; hospital mortality 20% vs 19%; P=0.73).

Exploratory secondary analyses did not identify any subgroups with potential benefit from the intervention. Finally there was no difference seen between intervention and control in the analysis of 20 patients' excretion of cortisol and melatonin metabolites.

Study critique

This study addresses an important question - delirium is both common and deleterious in the ICU population. The intervention had biological plausibility, an appropriately sized and defined study population was chosen, the intervention was effectively applied and outcomes were properly assessed in all patients. This allows confidence in their finding, that DLA as applied did not have a beneficial effect in their hospital's ICU population: this was a successful negative trial.

Aspects of the methodology are especially worthy of praise; for example, it is known that delirium assessment by the CAM-ICU is imperfect: In a Dutch study conducted in 10 ICUs who all routinely used CAM-ICU 2-3 times per day, experts validated 282 delirium assessments by bedside nurses and calculated the sensitivity of CAM-ICU in routine use to be 47%, specificity was good at 98%.⁴ This suggests delirium is rarely mis-diagnosed but missed by half of individual assessments in routine practice. In this study the investigators confirmed the validity of CAM-ICU results by 2-monthly assessments of inter-observer reliability, and the research setting may have further improved accuracy. There still may have been cases missed by individual nurses but it seems unlikely many episodes of significant duration weren't captured.

There is also little doubt about the dose of DLA given; as well as achieving 100% adherence to the lighting protocol, the investigators also measured the light intensity using photometers recording data every 15 minutes, from which the mean hourly illuminance received was recorded for all patients. This ensured the light intensity was comparable to that used in previous successful trials in the non-ICU setting.⁵ One potential (acknowledged) issue is that the therapy was presumably given through mostly



closed eyes in the early stages of ICU admission - 65% of patients were intubated and use of sedatives was high. This may have limited the stimulation of retinal photosensitive cells which are linked to the hypothalamic control of melatonin secretion.⁶

As this was conducted in a single ICU there may have been centre-specific factors that prevented the therapy from exhibiting a beneficial effect; for example, the sedation practice beyond admission is not well described. The case-mix, however, seems comparable to other general ICUs and there is no evidence the care given in the facility was in any way substandard. Although the authors comment that 95% of patients were exposed to natural daylight through adjacent windows, this study does not exclude a benefit of DLA in centres without that luxury; but again, there was no evidence of a seasonal variation in delirium rates which could have suggested this was an important factor.

The measurement of hormone levels allows insights into the putative mechanism of action of the therapy as well as its effects. The data suggest melatonin secretion was low overall and did not vary from night to day; i.e., the normal circadian rhythm was lost, which has been previously demonstrated in ICU populations.^{7,8} It may be this is an inherent feature of the early stage of critical illness and systemic inflammation, and may not be easy to correct. It would have been preferable to have a larger subset of participants contribute to this part of the study to increase confidence in the finding.

There was no evidence of harm and DLA may be worthy of future study. Based on the findings of this trial, this could involve DLA in combination with nocturnal melatonin. It could be commenced after the initial phase of ICU admission when sedative infusions were reduced or discontinued, eyes are open and the first stage of systemic inflammation / immune dysregulation may have peaked.

Where this sits in the body of evidence

Prior evidence for bright light therapy in ICU patients is limited to two small Japanese RCTs of post-oesophagectomy patients.^{9,10} There were methodological issues including the exclusion of patients intolerant of the therapy from analysis. The results were collated in a review of post-operative attempts to reduce delirium.¹¹ The trials were rated as of moderate quality (Jadad score 3 in each). A total of 33 patients were included, with delirium diagnosed in 2 intervention patients and 7 control (OR 0.2; 95% CI, 0.03 – 1.19; P=0.08).

In 2001 Ely et al prospectively tested the CAM-ICU tool in 111 consecutive mechanically ventilated patients.¹² When compared to assessment by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSMD) delirium criteria, the CAM ICU performed by 2 study nurses had a sensitivity, specificity and inter-rater reliability of >90% for the diagnosis of delirium.



In 1999, Inouye, in a prospective non-randomised cohort study examined the effect of a multifaceted intervention targeting cognitive impairment, sleep deprivation, immobility, visual and hearing impairment and dehydration (Hospital Elder Life Program, HELP) in elderly general medical patients.² 426 subjects were compared with 426 concurrently enrolled controls admitted to different units. The intervention group had a reduced incidence and duration of delirium (incidence 9.9 vs 15.0%; 95% CI, 0.39 to 0.92; P=0.02; total days with delirium 105 vs 161 days; P=0.02).

In 2008, Riemersma-van der Lek et al conducted a 2 X 2 factorial randomised controlled trial studying bright light therapy (± 1000 lux) and melatonin (2.5mg) against low light therapy (± 300 lux) and placebo.⁵ 189 residents of elderly care homes were included for up to 3 years. Light therapy attenuated deterioration in Mini-Mental State Examination scores by 5%. Melatonin improved sleep quality but caused a deterioration in mood disorders if given without light therapy.

In 2013, Chong et al reported on 228 patients with delirium who had been admitted to a specialist Geriatric Medicine Unit in Singapore.¹³ There was no control group. Light therapy (2-3000 lux) was administered for 4 hours daily alongside a multicomponent delirium management programme. Clinical improvements were seen in sleep quality during admission.

In 2012, Van Rompaey et al randomised 136 Antwerp ICU patients to sleeping with or without earplugs (33 dB reduction).³ They were inserted from 2200 h until 0600 h and concealed from the investigators performing sleep quality and delirium assessments. Delirium was assessed using the NEECHAM score, previously validated in Flemish populations. There was no difference in the rates of delirium (with earplugs 20.3% vs 19.4% without). There was a significant reduction with earplugs in the NEECHAM category "mild confusion" (14.5% vs 40.3%; HR 0.47; 95% CI, 0.27 to 0.82; P=0.008); the implications of which are uncertain. Sleep quality was significantly better with earplugs (P=0.042).

Should we implement this into our practice?

No. There was no evidence of benefit of Dynamic Light Application therapy in this well-run study.

References

1. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *Lancet Lond Engl* 2014;383(9920):911–22.
2. Inouye SK, Bogardus ST, Charpentier PA, et al. A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients. *N Engl J Med* 1999;340(9):669–76.
3. Van Rompaey B, Elseviers MM, Van Drom W, Fromont V, Jorens PG. The effect of earplugs during the night on the onset of delirium and sleep perception: a randomised controlled trial in intensive care patients. *Crit Care* 2012;16(3):R73.
4. van Eijk MM, van den Boogaard M, van Marum RJ, et al. Routine use of the confusion assessment method for the intensive care unit: a multi-centre study. *Am J Respir Crit Care Med* 2011;184(3):340–4.
5. Riemersma-van der Lek RF. Effect of Bright Light and Melatonin on Cognitive and Noncognitive Function in Elderly Residents of Group Care Facilities: A randomised Controlled Trial. *JAMA* 2008;299(22):2642.
6. Annane D. Light therapy and chronobiology in critical illness. *Lancet Respir Med* 2016;4(3):167–8.
7. Mundigler G, Delle-Karth G, Koreny M, et al. Impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. *Crit Care Med* 2002;30(3):536–40.
8. Olofsson K, Alling C, Lundberg D, Malmros C. Abolished circadian rhythm of melatonin secretion in sedated and artificially ventilated intensive care patients. *Acta Anaesthesiol Scand* 2004;48(6):679–84.
9. Ono H, Taguchi T, Kido Y, Fujino Y, Doki Y. The usefulness of bright light therapy for patients after oesophagectomy. *Intensive Crit Care Nurs* 2011;27(3):158–66.
10. Taguchi T, Yano M, Kido Y. Influence of bright light therapy on post-operative patients: A pilot study. *Intensive Crit Care Nurs* 2007;23(5):289–97.
11. Moyce Z, Rodseth RN, Biccand BM. The efficacy of peri-operative interventions to decrease post-operative delirium in non-cardiac surgery: a systematic review and meta-analysis. *Anaesthesia* 2014;69(3):259–69.
12. Ely EW, Inouye SK, Bernard GR, et al. Delirium in Mechanically Ventilated Patients: Validity and Reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *JAMA* 2001;286(21):2703.
13. Chong MS, Tan, Tay, Wong, Ancoli-Israel S. Bright light therapy as part of a multicomponent management program improves sleep and functional outcomes in delirious older hospitalized adults. *Clin Interv Aging* 2013;565.



Circulatory Trials



ALPS

Kudenchuk PJ, Brown SP, Daya M, Rea T, Nichol G, Morrison LJ, et al.
Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest. *N Engl J Med* 2016;374(18):1711–22

Introduction

Clinicians who treat cardiac arrest patients aim to produce survivors with good neurological outcomes. A focus on early, high quality cardiopulmonary resuscitation (CPR), where interruptions are minimised, has resulted in improved rates of survival from out-of-hospital cardiac arrest (OHCA) over time.¹ The OPALS study demonstrated that the implementation of pre-hospital advanced life support, including drugs and endotracheal intubation, conferred no benefit in survival-to-hospital discharge or neurological recovery compared to CPR and defibrillation only.² There is a large and consistent body of evidence demonstrating pharmacological interventions do not improve survival-to-hospital discharge; drugs such as adrenaline, vasopressin, amiodarone, lidocaine, sodium bicarbonate and cyclosporine have all failed to show benefit in this outcome measure.³⁻⁸ Even adrenaline, the cornerstone of pharmacotherapy for cardiac arrest management, does not out-perform placebo in terms of survival-to-hospital discharge.³

The use of anti-arrhythmics in OHCA due to ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) has consistently been shown to increase rates of survival-to-hospital admission and return of spontaneous circulation (ROSC).^{5,6} However, these trials have not been powered to detect differences in survival-to-hospital discharge, a more patient-centred outcome.^{5,6} The ALPS trial sought to address this by investigating the effect of amiodarone, lidocaine or placebo on rates of survival-to-hospital discharge.

Study synopsis

This American, multi-centre, randomised, double-blind trial compared the effects of IV amiodarone, lidocaine, and placebo on survival-to-hospital discharge in patients with out-of-hospital non-traumatic cardiac arrest due to shock-refractory VF or pulseless VT. This was defined as non-terminating or recurrent (restarting after successful termination) VF or pulseless VT after defibrillation at any point during resuscitation. Patients were required to be aged > 18 years and have IV or intra-osseous access. Patients who had received open label lidocaine or amiodarone were excluded.

The intervention consisted of standard resuscitation based on American Heart Association guidelines. After failure of one or more shocks to successfully terminate VF or pulseless VT, patients were administered the trial drug. Trial drugs were in identical syringes, containing either 150 mg of amiodarone, 60 mg of lidocaine or 3 mLs of saline. Two syringes of trial drug were administered initially; if the patients remained in VF or



pulseless VT one further syringe of trial drug could be administered. If further anti-arrhythmics were needed open label amiodarone and lidocaine was used. In hospital management of patients was recorded but not standardised.

Trial drugs were randomly distributed to EMS providers in a 1:1:1 ratio. Randomisation was performed in permuted blocks with stratification according to participating site and EMS agency. The primary outcome measure was survival-to-hospital discharge. Secondary outcomes measures included survival with a favourable neurological outcome, defined as a modified Rankin Scale of 3 or less. The trial design stated that the primary analysis would be carried out on the per-protocol population, however, analysis of the intention-to-treat population was also carried out.

Power calculations were based on the comparison of amiodarone with placebo, with an assumed baseline survival of 29.7% in the amiodarone group. The authors estimated a sample size of 3000 patients in the per-protocol population (1000 patients per group) would provide 90% power to detect an absolute difference of 6.3% in the rate of survival-to-hospital discharge. For the primary outcome measure, a one-sided significance level of 0.025 was used when comparing active drug and placebo and a two-sided significance level of 0.05 when comparing amiodarone with lidocaine.

37,889 patients were assessed, with 7051 being eligible for entry into the trial. 4653 patients were included in the intention-to-treat analysis and 3026 in the per-protocol analysis. The data presented here is from the per-protocol analysis. The three groups were well balanced at baseline. Approximately 60% of patients had bystander initiated CPR.

survival-to-hospital discharge was 24.4% in the amiodarone group, 23.7% in the lidocaine group and 21.0% in the placebo group. There was no statistically significant difference in survival-to-hospital discharge between any of the groups. There was no significant differences between rates of favourable neurological outcome; amiodarone group (18.8%), lidocaine (17.5%), and placebo group (16.6%). Pre-specified subgroup analysis of patients with bystander witnessed cardiac arrest demonstrated improved survival with active drugs compared to placebo; amiodarone (27.7%), lidocaine (27.8%) compared to placebo (22.7%). This absolute difference in survival was significant for amiodarone versus placebo (5.0%; 95% CI, 0.3 to 9.7; P=0.04) and for lidocaine versus placebo (5.2%; 95% CI, 0.5 to 9.9; P=0.03) but not for amiodarone versus lidocaine (P = 0.97). In contrast, there was no difference in survival for patients who suffered unwitnessed OHCA.

Rates of ROSC were higher in the lidocaine group (39.9%) than in the amiodarone group (35.9%) and placebo group (34.6%). Patients treated with lidocaine were statistically more likely than those treated with placebo to achieve ROSC (absolute difference 5.4%; 95% CI 1.2 to 9.5%, P=0.01). Other between group comparisons for rates of ROSC did

not reach statistical significance. More patients in the amiodarone group (45.7%; $P=0.01$) and in the lidocaine group (47.0%, $P<0.001$) survived to hospital admission than the placebo group (39.7%); comparisons are for amiodarone and lidocaine versus placebo, respectively. The risk of suffering any adverse event was similar in all three groups. However, the need for temporary pacing in the first 24 hours was significantly higher in the amiodarone group (4.9%) than the lidocaine group (3.2%) or placebo groups (2.7%). The amiodarone group also had a higher use of atropine pre-hospital ($P=0.04$).

Study critique

The ALPS trial was a randomised, controlled trial examining the effect on survival-to-hospital discharge of different anti-arrhythmic drugs in OHCA.⁹ This trial was carried out by the Resuscitation Outcomes Consortium Investigators, the group also responsible for trials into continuous versus interrupted CPR, ROC PRIMED trial and major observational studies into cardiac arrest outcomes.^{1,9-12} Previous work by this group had strict quality controls in place; indeed, a number of the patients were co-enrolled into another trial.¹⁰ This appeared to be a well conducted trial. The high chest compression fraction (the proportion of time spent during each minute performing chest compressions) of 0.83 and the high rate of successful advanced airway management in the pre-hospital phase (over 84%) are indicative of high quality care.¹²

Despite the well designed trial and high degree of quality control, approximately one third of patients were excluded from the per-protocol analysis. The majority of patients who were excluded, 1063 of 1627 patients, had an initial non-shockable rhythm. This, accompanied with the fact that only 7051 of the 37,889 patients screened were eligible, means the results presented will not be applicable to a large number of patients. This emphasises the difficulties in running a randomised controlled trial in cardiac arrest in the pre-hospital setting. Furthermore, the trial was slightly underpowered as the predicted survival was 29.7% in the amiodarone group but the observed survival was 24.4%.

Previous studies have demonstrated the short term benefit of anti-arrhythmics on increasing rates of ROSC and improving survival-to-hospital admission.^{5,6} The findings of the ALPS trial are consistent with this body of evidence demonstrating that amiodarone and lidocaine are effective anti-arrhythmics. Patients who were allocated to receive placebo were more likely to require all three syringes of the trial drug (72.1%) than those allocated to amiodarone (64.2%) or lidocaine (60.6%). In addition, those in the placebo group required a greater number of shocks post enrolment; a median of 3 compared to 2 in both the amiodarone and lidocaine groups ($P < 0.001$). The placebo group was also more likely to require additional anti-arrhythmic medication in the form of procainamide and magnesium in hospital. This resulted in more patients treated with active drug surviving to hospital admission, with fewer re-arrests in hospital.



The question arises, if amiodarone and lidocaine are effective anti-arrhythmics which increase rates of survival-to-hospital admission, and decrease rates of re-arrest, why was no benefit seen in survival-to-hospital discharge? The authors comment that the lower than anticipated differences in mortality between the amiodarone and placebo groups leaves the study ultimately underpowered and that a trial involving 9000 patients would be required to detect a 3% difference in mortality. The differences in mortality between the amiodarone and placebo groups are even less in the intention-to-treat population; just 1.4%. Moreover, the difference in rates of survivors with good neurological outcome is just 0.6% between the amiodarone and placebo groups in the intention-to-treat population. On this basis, it seems anti-arrhythmics offer no benefit in survival-to-hospital discharge, again a feature consistent with the body of evidence.^{5,6}

It is likely that early into cardiac arrest an inflammatory process ensues which is difficult to reverse with a limited pre-hospital intervention such as an anti-arrhythmic agent.^{9,13} Weisfeldt and Becker describe a “metabolic phase”, beginning after approximately 10 minutes of cardiac arrest, characterised by tissue injury from global ischaemia and reperfusion injuries.¹³ It is noteworthy the mean time to first administration of the trial drug was 19.3 ± 7.4 minutes after the initial call to emergency medical services. Other trials looking at pre-hospital interventions in OHCA, such as mechanical CPR devices, continuous CPR versus CPR interrupted for ventilation, and defibrillation during mechanical CPR, have all reported no difference in outcome.^{10,14-16} However, early bystander CPR and early defibrillation, i.e. interventions prior to the onset of the metabolic phase, are associated with improved survival-to-hospital discharge.^{2,17,18} Overall, outcomes from cardiac arrest remain poor and although anti-arrhythmics offer a short term survival benefit with little evidence of harm, on current evidence they do not influence survival-to-hospital discharge.

Where this sits in the body of evidence

In a randomised controlled trial 300 mg of amiodarone was compared to placebo in 504 patients with shock refractory VF or pulseless VT. Of those treated with amiodarone 44% survived to hospital admission compared to 34% treated with placebo; $P=0.03$ (adjusted OR, 1.6; 95% CI, 1.1 to 2.4; $P=0.02$). survival-to-hospital discharge, a secondary outcome measure, did not differ between the two groups; 13.4% in the amiodarone group versus 13.2% in the placebo group.⁵

The ALIVE trial randomised 347 patients with shock refractory VF or pulseless VT to receive either IV lidocaine or IV amiodarone. 22.8% of patients treated with amiodarone survived to hospital admission, compared to 12.0% of patients treated with lidocaine (OR, 2.17; 95% CI, 1.21 to 3.83, $P=0.009$). Patients in whom VF was their initial presenting rhythm had higher rates of survival-to-hospital admission than those who had a non-shockable rhythm and went on to develop VF (19.6% vs 8.2%; $P<0.05$). Only 5% of patients in the amiodarone group survived to hospital discharge compared to 3% in the



lidocaine group.⁶

In a small randomised, controlled trial of 29 patients with shock refractory VT who had maintained their cardiac output, IV amiodarone 150 mg was compared to IV lidocaine 100 mg. Patients were given up to two doses followed by a cardioversion if VT persisted. 78% of patients in the amiodarone group, compared to 27% of patients in the lidocaine group had successful termination of their VT ($P < 0.05$).¹⁹

In a prospective, randomised, controlled trial involving 851 patients, standard advanced cardiac life support (ACLS) with IV drug administration (control group) was compared to ACLS without drug administration (intervention group). There was no difference in the primary outcome measure of survival-to-hospital discharge; 10.5% in the control group compared to 9.2% in the intervention group (OR, 1.16; 95% CI, 0.74 to 1.82; $P = 0.61$). There was no difference in survival with favourable neurological outcome (OR, 1.24; 95% CI, 0.77 to 1.98; $P = 0.45$). However, those in the control group had better short term outcomes with 40% achieving ROSC compared to 25% in the intervention group (OR, 1.99; 95% CI, 1.48 to 2.67; $P = 0.001$) and 43% compared to 29% being admitted to the hospital (OR, 1.81; 95% CI, 1.36 to 2.40; $P = 0.001$).²⁰

A trial from West Australia randomised 534 patients with OHCA to receive either 1 mg of adrenaline or placebo. There was no statistically significant difference in the primary outcome measure of survival-to-hospital discharge; this occurred in 5 (1.9%) patients in the placebo group and 11 (4.0%) patients in the adrenaline group (OR, 2.2; 95% CI, 0.7 to 6.3; $P = 0.15$). ROSC was obtained in 8.4% of patients in the placebo group and 23.5% of those in the adrenaline group (OR, 3.4; 95% CI, 2.0 to 5.6; $P < 0.001$).³

Wenzel and colleagues undertook a randomised controlled trial comparing two doses of 40 units of vasopressin with two doses of 1 mg of adrenaline in 1186 patients with OHCA. There was no difference between vasopressin and adrenaline in the primary endpoint of survival-to-hospital admission in patients with VF (46.2% vs 43.0%, $P = 0.48$) or pulseless electrical activity (33.7% vs 30.5%, $P = 0.65$). However, in those with asystole, 29.0% of those treated with vasopressin survived to hospital admission, compared to 20.3% of those treated with adrenaline ($P = 0.02$).⁴

An older study, which ran between 1983 and 1985, randomised 373 patients with VF to epinephrine or lidocaine. During this time, defibrillation was delivered in three stacked shocks, making this trial less relevant to current clinical practice. Patients received either 0.5 mg epinephrine or lidocaine 100 mg after the first defibrillation if they remained in VF. The dose was repeated after the second shock if needed. There was no difference in rates of survival-to-hospital discharge between the two groups; 20% in the lidocaine group, compared to 19% in the epinephrine group. Sodium bicarbonate, which had been given in historical controls did not improve survival-to-hospital discharge.⁷



Should we implement this into our practice?

Yes. anti-arrhythmics offer short term benefits with little evidence of harm but do not confer any long term survival advantage.

References

1. Daya MR, Schmicker RH, Zive DM, Rea TD, Nichol G, Buick JE, et al. Out-of-hospital cardiac arrest survival improving over time: Results from the Resuscitation Outcomes Consortium (ROC). *Resuscitation*. 2015 Jun;91:108–15.
2. Stiell IG, Wells GA, Field B, Spaite DW, Nesbitt LP, De Maio VJ, et al. Advanced Cardiac Life Support in Out-of-Hospital Cardiac Arrest. *New England Journal of Medicine*. 2004 Aug 12;351(7):647–56.
3. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. *Resuscitation*. 2011 Sep;82(9):1138–43.
4. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH. A Comparison of Vasopressin and Epinephrine for Out-of-Hospital Cardiopulmonary Resuscitation. *New England Journal of Medicine*. 2004 Jan 8;350(2):105–13.
5. Kudenchuk PJ, Cobb LA, Copass MK, Cummins RO, Doherty AM, Fahrenbruch CE, et al. Amiodarone for Resuscitation after Out-of-Hospital Cardiac Arrest Due to Ventricular Fibrillation. *New England Journal of Medicine*. 1999 Sep 16;341(12):871–8.
6. Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as Compared with Lidocaine for Shock-Resistant Ventricular Fibrillation. *New England Journal of Medicine*. 2002 Mar 21;346(12):884–90.
7. Weaver WD, Fahrenbruch CE, Johnson DD, Hallstrom AP, Cobb LA, Copass MK. Effect of epinephrine and lidocaine therapy on outcome after cardiac arrest due to ventricular fibrillation. *Circulation*. 1990 Dec 1;82(6):2027–34.
8. Argaud L, Cour M, Dubien P, et al. Effect of cyclosporine in nonshockable out-of-hospital cardiac arrest: The cyrus randomised clinical trial. *JAMA Cardiol*. 2016 Aug 1;1(5):557–65.
9. Joglar JA, Page RL. Out-of-Hospital Cardiac Arrest — Are Drugs Ever the Answer? *New England Journal of Medicine*. 2016 May 5;374(18):1781–2.
10. Nichol G, Leroux B, Wang H, Callaway CW, Sopko G, Weisfeldt M, et al. Trial of Continuous or Interrupted Chest Compressions during CPR. *New England Journal of Medicine*. 2015 Dec 3;373(23):2203–14.
11. Cheskes S, Schmicker RH, Verbeek PR, Salcido DD, Brown SP, Brooks S, et al. The



- impact of peri-shock pause on survival from out-of-hospital shockable cardiac arrest during the Resuscitation Outcomes Consortium PRIMED trial. *Resuscitation*. 2014 Mar 1;85(3):336–42.
12. Christenson J, Andrusiek D, Everson-Stewart S, Kudenchuk P, Hostler D, Powell J, et al. Chest Compression Fraction Determines Survival in Patients with Out-of-hospital Ventricular Fibrillation. *Circulation*. 2009 Sep 29;120(13):1241–7.
 13. Weisfeldt ML, Becker LB. Resuscitation after cardiac arrest: A 3-phase time-sensitive model. *JAMA*. 2002 Dec 18;288(23):3035–8.
 14. Wik L, Olsen J-A, Persse D, Sterz F, Lozano M, Brouwer MA, et al. Manual vs integrated automatic load-distributing band CPR with equal survival after out-of-hospital cardiac arrest. The randomised CIRC trial. *Resuscitation*. 2014 Jun 1;85(6):741–8.
 15. Perkins GD, Lall R, Quinn T, Deakin CD, Cooke MW, Horton J, et al. Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial. *The Lancet*. 2015 Mar;385(9972):947–55.
 16. Rubertsson S, Lindgren E, Smekal D, et al. Mechanical chest compressions and simultaneous defibrillation vs conventional cardiopulmonary resuscitation in out-of-hospital cardiac arrest: The LINC randomised trial. *JAMA*. 2014 Jan 1;311(1):53–61.
 17. Wissenberg M, Lippert FK, Folke F, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. *JAMA*. 2013 Oct 2;310(13):1377–84.
 18. Valenzuela TD, Roe DJ, Nichol G, Clark LL, Spaite DW, Hardman RG. Outcomes of Rapid Defibrillation by Security Officers after Cardiac Arrest in Casinos. *New England Journal of Medicine*. 2000 Oct 26;343(17):1206–9.
 19. Somberg JC, Bailin SJ, Haffajee CI, Paladino WP, Kerin NZ, Bridges D, et al. Intravenous lidocaine versus intravenous amiodarone (in a new aqueous formulation) for incessant ventricular tachycardia. *Am J Cardiol*. 2002 Oct 15;90(8):853–9.
 20. Olasveengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA, Wik L. Intravenous drug administration during out-of-hospital cardiac arrest: a randomised trial. *JAMA*. 2009 Nov 25;302(20):2222–9.



RINSE

Bernard SA, Smith K, Finn J, Hein C, Grantham H, Bray JE, et al. Induction of Therapeutic Hypothermia During Out-of-Hospital Cardiac Arrest Using a Rapid Infusion of Cold Saline: The RINSE Trial (Rapid Infusion of Cold Normal Saline). *Circulation* 2016;13;134(11):797-805

Introduction

In the UK there are approximately 30,000 cases of out-of-hospital cardiac arrest (OHCA) each year.¹ Rates of survival-to-hospital discharge range from 2-12%.² Patients admitted to ICU following OHCA may develop cerebral dysfunction due to anoxic injury and as part of a post cardiac arrest syndrome. The ensuing brain injury is responsible for 68% of the deaths that occur in ICU.³ Of those who survive, 11% are left severely disabled or in a vegetative state.^{3,4} In patients who achieve return of spontaneous circulation (ROSC), therapeutic hypothermia may decrease cerebral oxygen demand. Two studies which cooled patients to 32-34°C demonstrated improved neurological outcomes and reduced mortality in comparison to usual care; however, the high rate of pyrexia in the usual care group has been a source of criticism.⁴⁻⁶ The largest trial of in-hospital cooling following OHCA has shown that avoiding hyperthermia by targeting a temperature < 36°C is equally as effective as maintaining temperature at 32-34°C.⁶ The 2015 European Resuscitation Guidelines now suggest the option to target 36°C or 32-34°C in the post resuscitation period, but stresses the importance of avoiding pyrexia.⁷

It appears rational that early cooling would provide greater neurological protection. Indeed, one of the original trials of therapeutic hypothermia began cooling patients pre-hospital, with the application of ice packs.⁴ There have been a number of subsequent studies in pre-hospital cooling. However, the three largest trials, which delivered ice cold fluids intravenously after ROSC, have failed to demonstrate any patient benefit.⁸⁻¹⁰

Study synopsis

The authors of the Rapid Infusion of cold Normal Saline (RINSE) trial hypothesised that administration of ice cold saline intravenously prior to ROSC would improve rates of ROSC and survival-to-hospital discharge. This multi-centre, randomised controlled trial was conducted across three major Australian cities where a number of different emergency medical service (EMS) models were in operation. At a minimum, paramedics could perform defibrillation, administer intravenous adrenaline and inset laryngeal mask airways. Patients in non-traumatic OHCA were eligible if ROSC had not been achieved after defibrillation for a shockable rhythm, intravenous access was obtained, one dose of epinephrine was delivered, and ventilation was ongoing with 100% oxygen. Exclusion criteria included EMS witnessed OHCA, pregnancy, suspected intra-cranial bleed and temperature <34.5 °C. Cardiac arrest management followed Australian Resuscitation



Council guidelines.

Patients were randomised to standard care or intra-arrest cooling achieved by a rapid infusion of 30 ml/kg cold saline intravenously at an approximate temperature of 3°C (maximum dose 2 L). The infusion was stopped if the patient's temperature was < 33°C or in cases of suspected pulmonary oedema. The standard care group could receive ambient temperature fluids during the arrest. In this pragmatic trial, in-hospital treatment was not standardised, but cooling to 33°C was standard care in many of the receiving ICUs.¹¹

Patients were randomised using computer-generated treatment allocation in the form of an opaque envelope which was opened by paramedics once the pre-conditions for eligibility were met. survival-to-hospital discharge was the primary outcome measure. Secondary outcome measures included discharge destination (home, rehabilitation or nursing facility), rates of ROSC for both shockable and non-shockable rhythms and tympanic temperature on arrival to hospital for those who achieved ROSC.

There were effectively two clinical trials running in parallel; one recruiting patients with a shockable rhythm, the other with a non-shockable rhythm.¹¹ Together these trials required 2,512 patients. The power calculation was based on assumptions derived from OHCA registry data. The authors predicted that half of all OHCA would be due to shockable rhythms and half due to non-shockable rhythms. Of all the patients who suffered an OHCA due to a shockable rhythm, it was predicted 40% would achieve ROSC with 20% surviving to hospital discharge. The authors proposed that intra-arrest cooling would improve outcomes in this group, with 45% achieving ROSC and 27% surviving to hospital discharge. The authors predicted 20% of all patients with non-shockable rhythms would achieve ROSC and 2% would survive to hospital discharge with intra-arrest cooling increasing survival-to-hospital discharge to 5%. After randomising 1324 patients, the trial was terminated prior to the first planned interim analysis due to the change of in hospital temperature management for OHCA patients in response to the TTM trial.⁶

During the trial period of December 2010 to December 2014, 22,775 patients suffered an OHCA, 11,476 were resuscitated but only 1,324 were recruited. The authors did not collect data to explain the reasons why 10,152 patients were not recruited. Of the 1,324 patients recruited, 122 met exclusion criteria and 4 refused permission for use of data. Ultimately, 1,198 were included in an "intention-to-treat analysis"; 618 in the intra-arrest cooling group and 580 into the standard care group.

The two groups were well balanced at baseline. A typical patient was a male in their mid sixties who arrested in a private residence. Overall, 60.7% of patients had a witnessed collapse, 66.5% of patients had bystander CPR, and 46.6% had a shockable rhythm. The



time from first call to arrival of a paramedic was approximately 9 minutes in both groups. The mean \pm SD baseline temperatures were $35.9 \pm 0.9^\circ\text{C}$ and $35.8 \pm 0.9^\circ\text{C}$ in the intra-arrest cooling and standard care groups, respectively. There were similar rates of intubation and number of defibrillations (7 ± 5) in both groups. Marginally more doses of epinephrine were administered in the intra-arrest cooling group (6.5 ± 3.8) than the standard care group (5.9 ± 3.6) ($P=0.006$), reflecting a longer duration of cardiac arrest in the intra-arrest cooling group (22.6 ± 11.5 min vs 20.0 ± 10.6 , $P=0.01$).

The intra-arrest cooling group received a mean of 1193 ± 647 ml of cold saline. There were 7 protocol violations in the standard care group resulting in a mean volume of cold saline administered of 15 mL ($P<0.001$). Including ambient temperature fluids, slightly more fluid was administered overall in the intra-arrest cooling group $1,380 \pm 773$ ml compared to $1,022 \pm 752$ ml in the standard care group ($P < 0.001$). The temperature on arrival to hospital for those with ROSC was lower in the intra-arrest cooling group; $34.7 \pm 1.2^\circ\text{C}$ vs $35.4 \pm 1.3^\circ\text{C}$ ($P < 0.001$).

There was no difference in the primary outcome measure of survival-to-hospital discharge; 10.2% vs 11.4% in the intra-arrest cooling and standard care groups, respectively ($P=0.51$). In subgroup analysis, there was no difference in survival-to-hospital discharge when those with shockable and non-shockable rhythms were examined. Only 3 patients out of 1,198 were discharged to a nursing care facility.

Among the secondary outcome measures, the intra-arrest cooling group had increased duration between arrival of EMS and achieving ROSC (22.6 min vs 20.0 min, $P=0.01$), increased rates of death at scene (50.8% vs 45.3%, $P=0.06$) and fewer patients transported with ROSC (33.5% vs 39.1% $P=0.04$). The poorer secondary outcomes seen in the intra-arrest cooling group were predominantly due to differences in the shockable rhythm cohort. Analysis of those with a shockable rhythm found that patients treated with intra-arrest cooling were more likely to die at the scene (44.3% vs 34.1% $P=0.01$) and less likely to be transported with ROSC (41.2% vs 50.6% $P=0.03$). In a subgroup analysis of those with a non-shockable rhythm, there was no difference between the standard care and intra-arrest cooling groups in relation to these secondary outcomes.

Study critique

This interesting pre-hospital study has a number of strengths. Although it was terminated early, it is the second largest trial investigating pre-hospital cooling. The challenges of conducting a trial in the fraught setting of OHCA cannot be underestimated. The quality of care was high as evidenced by the survival rate of 10.8%.¹² It was randomised, and by running effectively two parallel studies, the authors sought to determine which patient group would benefit from this intervention; those with a shockable rhythm (who are more likely to have a cardiac cause of their arrest) or those with a non-shockable rhythm.¹¹

This trial was the first large study to give intravenous ice cold fluids intra-arrest, therefore, it addressed a subtly different question than studies which had only applied this intervention after ROSC.⁸⁻¹⁰ Previous trials had generated the question, is the administration of ice cold fluid following ROSC too late to stem the inflammatory cascade? Also, previous trials often did not administer the volume of fluid targeted pre-hospital due to the short duration between achieving ROSC and arriving at hospital.⁸⁻¹⁰ Moreover, previous control groups were treated with 40 ml/kg ice cold fluids in the emergency department, resulting in no temperature difference between groups 60 minutes after arriving in the emergency department.^{9,10} This resulted in a small window in which pre-hospital treatment with ice cold fluids could provide a benefit over usual care. By administering ice cold fluids earlier this trial had the potential to address these questions.

Despite the earlier intervention, the volume of cold saline administered was small (1193 ± 647 ml) and lower than previous studies achieved.⁹ The between group separation of just 0.7°C may reflect under dosing of ice cold fluids. In addition, “ice cold” fluids stored in refrigeration devices in ambulances may be as warm as 11°C.¹³ This exemplifies the tremendous challenges faced conducting trials in the pre-hospital environment.

During the trial period, the in-hospital management of OHCA patients consisted of administration of 40 ml/kg ice cold fluid. The changes in clinical practice in response to the TTM trial would have likely introduced a confounding variable.⁶ On this basis, the trial management committee took the pragmatic decision to terminate the trial having enrolled 1,198 of the planned 2,512 patients. The power calculations of this trial warrant discussion. Notably, the trial was powered based on a 7% absolute increase in survival in the shockable group (from 20% to 27%) and a 3% absolute increase in survival in the non-shockable group (from 2% to 5%). These both seem ambitious. In addition, the statistical plan, published in 2011, states the increase in ROSC and survival in the shockable rhythm group was based on laboratory data.¹¹ However, by 2010 two phase III trials looking at pre-hospital cooling using ice cold fluids following ROSC and a feasibility study involving intra-arrest cooling using a nasal device had been published.^{9,10,14} These trials had all failed to demonstrate a difference in outcomes. Ultimately, in the recruited patients, the only signal apparent was one of harm from cooling.

Intra-arrest cooling applied to patients with a shockable rhythm was associated with a prolonged duration of cardiac arrest and a higher risk of death at scene. The authors postulate a number of potential reasons for this. One such cause was the intervention may have interfered with resuscitation efforts. Ice cold saline was administered after the first dose of epinephrine i.e. early in arrest cycle therefore potentially delaying defibrillation or increasing peri-shock pauses when the myocardium has greatest chance of successful defibrillation.¹⁵ However, ice cold fluid administered after ROSC has been

achieved is also associated with a higher rate of rearrest at the scene.⁸ This suggests that a factor other than changes in intra-arrest management was responsible.

The way in which the cold saline was administered may have produced this finding. Neither the RINSE trial or its previously published methodology described how the cold saline would be administered simply stating it was given “stat” (in comparison, the control group could have a “fluid challenge” administered).¹¹ Two previous trials studying pre-hospital cooling conducted by the same authors used ice cold fluids pressurised to 300 mm Hg.^{9,10} Fluid resuscitation in cardiac arrest causes an increase in right atrial pressure without an increase in aortic diastolic pressure, hence overall coronary artery perfusion pressure is decreased.^{16,17} In a study of patients with cardiac arrest, coronary perfusion pressure was the factor most predictive of ROSC, and only patients with a coronary perfusion pressure of ≥ 15 mm Hg achieved ROSC.¹⁸ Animal models have shown that rapid infusion of 1,000 ml of fluid results in a decrease in left ventricular myocardial blood flow from 12.0 to 4.1 ml/min/100 g ($P < 0.05$).¹⁹

The authors conducted post hoc analysis in an effort to explore reasons for the poorer outcomes in patients with shockable rhythm treated with cold saline. They examined whether the additional volume of fluid administered in the intra-arrest cooling group was responsible. They found that adjustment for total volume of fluid given did not change the chances of death at the scene (OR, 1.43; 95% CI, 1.00 to 2.04, $P=0.05$), i.e. the finding was due to intra-arrest cooling not volume of fluid administered.

The trial suffers other limitations also. There was no blinding. Only 10.4% of patients screened were recruited. As the authors cannot attest to the reasons for excluding 90% of patients it would have been hard to apply any findings to a wider OHCA population. Overall this was an interesting study which adds to the growing body of evidence that pre-hospital cooling using rapid infusion of cold fluids is unhelpful and may be harmful.

Where this sits in the body of evidence

In a study of 1,359 patients with OHCA who achieved ROSC, participants were randomised to standard care or 2000 ml of IV saline at 4°C. Patients were stratified into those with VF and those without. IV cold saline decreased patient temperature by 1.2 to 1.3°C and reduced the mean time to reach 34°C ($P<0.001$). There was no difference in the primary outcome measure of survival-to-hospital discharge; in those with VF, cold saline group 62.7% (95% CI, 57.0% to 68.0%) vs control group 64.3% (95% CI, 58.6% to 69.5%) ($P=0.69$); in those without VF; cold saline group 19.2% (95% CI, 15.6% to 23.4%) vs control group 16.3% (95% CI, 12.9% to 20.4%) ($P=0.30$). There was no difference in neurological outcome. There was a higher incidence of rearrest during transport in the cold saline group (26% compared to 21% in the control group, $P=0.008$).⁸

The RICH trial randomised 234 patients who had suffered an OHCA due to VF / pulseless



VT and achieved ROSC to either pre-hospital cooling (2000 ml of intravenous ice cold lactated Ringer's solution) or in-hospital cooling (40 mL/kg intravenous ice cold lactated Ringer's solution).^{9,10} Surface cooling to 33°C was standard for all patients once in ICU. The intervention caused a mean decrease in temperature of 0.8°C (P=0.01). However, the temperature in both groups was 34.7°C after 60 minutes in the emergency department (P=0.70). There was no difference in rates of discharge alive with a favourable neurological outcome; 47.5% in the pre-hospital cooling group compared to 52.6% in the in-hospital cooling group (RR, 0.90; 95% CI, 0.70 to 1.17, P=0.43). The study was terminated early due to futility after recruiting 234 of a planned 372 patients.⁹

In a trial which ran concurrently with the RICH trial, 163 patients with OHCA who had ROSC following asystole or PEA were randomised to pre-hospital cooling with 40 ml/kg (maximum 2 L) of intravenous ice cold Hartmann's solution (pressurised to 300 mm Hg at 100 ml/min) or cooling on arrival to hospital.⁹ The in-hospital management was similar to the RICH trial.⁹ The pre-hospital cooling group had a mean temperature drop of 1.4°C. There was no difference in the primary outcome measure of discharge alive with a good neurological outcome; 12% vs 9% in the pre-hospital cooling and in-hospital cooling groups, respectively (P=0.50). The target recruitment was 398 patients. The RICH trial was terminated early, and for logistical reasons, this trial was also terminated.¹⁰

PRINCE was a prospective trial which randomised 200 patients with OHCA to intra-arrest cooling using the RhinoChill device (BeneChill, Inc, San Diego, California) or standard care prior to ROSC. This was designed as a feasibility study and was not powered to detect differences in outcome. Intra-nasal cooling resulted in a significantly lower temperature on arrival to hospital (34.2°C vs 35.5°C, P<0.001). The median time to reach 34°C was significantly shorter in the intra-nasal cooling group (102 min vs 291 min, P=0.03). There was no difference in rates of ROSC (38% vs 43% in the treatment and standard care groups, respectively; P=0.48) or discharge neurologically intact (34.4% vs 21.4%, P=0.21).¹⁴

The TTM trial compared in-hospital cooling to 33°C with 36°C in 950 patients who had suffered an OHCA (irrespective of rhythm) and had a GCS < 8. The cooling intervention lasted for 24 hours and temperature was controlled to < 37.5°C for 72 hours. Cooling could be achieved by intravenous ice cold fluids, application of ice packs or commercially available cooling devices. There was significant separation between the temperature curves for the two groups (P<0.001). There was no difference in end-of-trial mortality; 50% in the 33°C group compared to 48% in the 36°C group (hazard ratio with a temperature of 33°C, 1.06; 95% CI, 0.89 to 1.28; P=0.51). There was no difference in the combined secondary outcome of death or poor neurological outcome at 180 days (RR in the 33°C group, 1.04; 95% CI, 0.89 to 1.17; P=0.67).⁶

Seventy seven patients with OHCA due to VF, who achieved ROSC but remained

comatose, were randomised to normothermia (target temperature 37°C) or cooling to 33°C. The intervention consisted of application of ice packs and began pre-hospital. Patients were cooled for 12 hours with active rewarming between hours 18 and 24. At six hours there was a large separation in temperature between the two groups (cooling group 32.7 ± 1.19°C vs normothermia group 37.1 ± 0.75°C, P<0.001). The primary outcome measure of survival to discharge with a good neurological outcome occurred in 49% of the treatment group and 26% of the standard care group (P = 0.046).⁴

The HACA study randomised 275 patients with OHCA due to VF / pulseless VT, who were unresponsive to voice after achieving ROSC, to therapeutic hypothermia or standard care. Therapeutic hypothermia, commenced in-hospital, was induced using cooling blankets and ice packs to target 32-34°C and maintained for 24 hours followed by 8 hours of passive rewarming. The primary endpoint of favourable neurological outcome was seen in 55% of the therapeutic hypothermia group compared to 39% in the normothermia group (RR, 1.40; 95% CI, 1.08 to 1.81). After adjustment for baseline imbalances, hypothermia was associated with a reduction in mortality (RR, 0.62; 95% CI, 0.36 to 0.95). Notably, the average temperature in the control group was consistently above 37°C from hours 8 to 48 after ROSC.⁵

Should we implement this into our practice?

No. There is no evidence to support cooling with intravenous cold saline in the pre-hospital setting. This practice may be harmful.

References

1. Perkins GD, Brace-McDonnell SJ, Group O behalf of the OP, Whittington A, Kaye C, Li C, et al. The UK out-of-hospital cardiac arrest Outcome (OHCAO) project. *BMJ Open*. 2015;5(10):e008736.
2. Perkins GD, Cooke MW. Variability in cardiac arrest survival: the NHS Ambulance Service Quality Indicators. *Emerg Med J*. 2012 Jan 1;29(1):3–5.
3. Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Böttiger BW, et al. Post-Cardiac Arrest Syndrome. *Circulation*. 2008 Dec 2;118(23):2452–83.
4. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia. *New England Journal of Medicine*. 2002 21;346(8):557–63.
5. HACA Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002 21;346(8):549–56.
6. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N*



- Engl J Med. 2013 Dec 5;369(23):2197–206.
7. Monsieurs KG, Nolan JP, Bossaert LL, Greif R, Maconochie IK, Nikolaou NI, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 1. Executive summary. *Resuscitation*. 2015 Oct;95:1–80.
 8. Kim F, Nichol G, Maynard C, Hallstrom A, Kudenchuk PJ, et al. Effect of pre-hospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomised clinical trial. *JAMA* 2014;311(1):45–52
 9. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomised controlled trial. *Circulation*. 2010 Aug 17;122(7):737–42.
 10. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, et al. Induction of pre-hospital therapeutic hypothermia after resuscitation from nonventricular fibrillation cardiac arrest*. *Crit Care Med*. 2012 Mar;40(3):747–53.
 11. Deasy C, Bernard S, Cameron P, Jacobs I, Smith K, Hein C, et al. Design of the RINSE trial: the rapid infusion of cold normal saline by paramedics during CPR. *BMC Emerg Med*. 2011 Oct 13;11:17.
 12. Perkins GD, Lall R, Quinn T, Deakin CD, Cooke MW, Horton J, et al. Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial. *The Lancet*. 2015 Mar;385(9972):947–55.
 13. Taskinen T, Puolakka J, Kuisma M. How cool are your “ice-cold” infusions? *Resuscitation*. 2010 Jul 1;81(7):921–2.
 14. Castrén M, Nordberg P, Svensson L, Taccone F, Vincent J-L, Desruelles D, et al. Intra-arrest transnasal evaporative cooling: a randomised, pre-hospital, multi-centre study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). *Circulation*. 2010 Aug 17;122(7):729–36.
 15. Cheskes S, Schmicker RH, Verbeek PR, Salcido DD, Brown SP, Brooks S, et al. The impact of peri-shock pause on survival from out-of-hospital shockable cardiac arrest during the Resuscitation Outcomes Consortium PRIMED trial. *Resuscitation*. 2014 Mar 1;85(3):336–42.
 16. Soar J, Foster J, Breitzkreutz R. Fluid infusion during CPR and after ROSC—is it safe? *Resuscitation*. 2009 Nov;80(11):1221–2.
 17. Yannopoulos D, Zviman M, Castro V, Kolandaivelu A, Ranjan R, Wilson RF, et al. Intra-cardiopulmonary resuscitation hypothermia with and without volume loading in an ischemic model of cardiac arrest. *Circulation*. 2009 Oct 6;120(14):1426–35.
 18. Paradis NA, Martin GB, Rivers EP, Goetting MG, Appleton TJ, Feingold M, et al.



Coronary Perfusion Pressure and the Return of Spontaneous Circulation in Human Cardiopulmonary Resuscitation. *JAMA*. 1990 Feb 23;263(8):1106–13.

19. Ditchey RV, Lindenfeld J. Potential adverse effects of volume loading on perfusion of vital organs during closed-chest resuscitation. *Circulation*. 1984 Jan 1;69(1):181–9.

CYRUS

Argaud L, Cour M, Dubien P, Giraud F, Jossan C, Riche B, et al. Effect of cyclosporine in nonshockable out-of-hospital cardiac arrest: The CYRUS randomised Clinical Trial. JAMA Cardiol 2016;1(5):557–65

Introduction

Cardiac arrest produces a global ischaemic insult with the return of circulation creating an ischaemia - reperfusion injury. The ensuing inflammatory cascade results in a post cardiac arrest syndrome characterised by brain injury, myocardial injury and potential multi-organ failure. It carries a high mortality, with 71% of patients admitted to ICU post cardiac arrest not surviving to hospital discharge.¹

One possible mechanism contributing to the post cardiac arrest syndrome is a change in mitochondrial permeability due to opening of the mitochondrial permeability transition pore (MPTP). Alterations in mitochondrial matrix pH and high matrix calcium concentration creates a chemical environment which predisposes the mitochondrial membrane to depolarisation and subsequent opening of the MPTP.^{2,3} Mitochondria begin to hydrolyse, as opposed to produce, adenosine triphosphate and lose the ability to maintain the normal mitochondrial electrochemical gradient.³⁻⁵ Mitochondrial swelling occurs with release of mediators of cell apoptosis.² cyclosporine may attenuate MPTP opening through inhibition of matrix cyclophilin D. Genetically engineered mice lacking the gene to produce cyclophilin D demonstrate a resistance to ischaemia - reperfusion injury.² Numerous triggering agents have been implicated in the opening of MPTP; the effect of cyclosporine on cyclophilin D only addresses one such pathway.^{4,6}

Study synopsis

This multi-centre, single-blind, randomised controlled trial tested whether administration of cyclosporine during an out-of-hospital cardiac arrest (OHCA) secondary to a non-shockable rhythm would reduce the incidence of multi-organ failure.

The emergency medical service (EMS) in France employs a two tier system. The first tier is made up of ambulances dispatched from fire stations, staffed by technicians who provide basic life support (BLS). The second tier consists of ambulances dispatched from hospitals, staffed by physicians who provide advanced cardiac life support (ACLS).⁷ In this trial, 16 hospitals and their respective EMS and ICUs participated.

Patients aged between 18 and 80 who suffered a witnessed OHCA were included if they presented with a non-shockable rhythm. Exclusion criteria included cardiac arrest duration > 30 minutes prior to treatment, trauma, pregnancy or cyclosporine allergy. Patients unlikely to survive based on co-morbidities were also excluded. Consecutive patients were randomised by the EMS dispatcher in a 1:1 fashion. There was



stratification based on centre.

The treatment consisted of cyclosporine 2.5 mg/kg administered as a single IV bolus as soon as practicable after commencing ACLS. In this open label study, the control group received no additional intervention (no placebo was used). Teams caring for the patients in hospital were not aware of the treatment assignment. In this pragmatic trial no other aspects of management were controlled, though the use of hypothermia was recorded.

Sequential Organ Failure Assessment (SOFA) score at 24 hours after hospital admission was the primary endpoint. SOFA scores measure six organ systems for dysfunction; each organ system is scored from 0 to 4, with a score of 3 or 4 indicating organ failure. Secondary endpoints included rates of return of spontaneous circulation (ROSC), rates of admission to hospital, SOFA score on admission, Glasgow Coma Scale score, need for organ support, survival at 24 hours, 7 days and 28 days, rates of discharge alive from hospital, and rates of favourable neurological outcome.

Given the early mortality associated with OHCA, 640 patients were required to be enrolled to have 128 patients alive at 24 hours, allowing the identification of a reduction in mean SOFA score of half the standard deviation at this time point, with 80% power and at the 5% significance level. Intention-to-treat (ITT) and per-protocol analyses were performed. A series of mixed-effect and fixed-effect models were used.

A total of 6,758 patients were assessed for eligibility and 737 eligible patients were missed. The majority of exclusions were for unwitnessed OHCA (2146), age outside eligibility criteria (2103) or shockable rhythm (806). 794 patients were enrolled, 24 were enrolled in error. Four hundred patients were allocated to the cyclosporine group and 394 to the control group. There was 100% follow up of patients.

The two groups were well balanced at baseline, with the exception of age (mean age 63.0 in the cyclosporine group versus 66.0 in the control group, $P=0.003$). Bystander CPR was performed in 43% of cases. The median duration of untreated cardiac arrest was 10 minutes and 19.0 minutes had elapsed prior to commencement of ACLS in both groups. The commonest presenting rhythm was asystole (85.5%) and the median total duration of ACLS was 40.0 minutes.

Of the 400 patients randomised to receive cyclosporine, 377 patients received the drug as planned. Nine patients in the control group received cyclosporine. The median time from collapse to administration of cyclosporine was 27.0 minutes.

129 patients survived to 24 hours and were included in the primary ITT analysis. The characteristics were well balanced between the two groups. The *median* SOFA scores at 24 hours were 10.0 (IQR, 7.0 to 13.0) versus 11.0 (IQR, 7.0 to 15.0) in the cyclosporine



and control groups respectively. Similarly, there was no difference in the predicted *mean* SOFA scores of these two groups; 10.1 (95% CI, 9.2 to 11.1) and 10.7 (95% CI, 9.7 to 11.7) respectively. Following a Box-Cox transformation of data to a normal distribution, there was no difference in the primary endpoint (P=0.45). The per-protocol analysis also showed no difference in outcome (P=0.51). Analysis was conducted to ascertain which variables would affect the SOFA scores at 24 hours; time to administration of cyclosporine, age, sex and duration of untreated OHCA had no effect on SOFA scores at 1 day. Only a long duration of ACLS affected SOFA scores at this time (P=0.002). When individual components of the SOFA score at 24 hours were examined, there was less respiratory failure in the cyclosporine group (34.3% vs 51.6%; P=0.05).

There was no difference in the use of target temperature management between the two groups. There was no difference in the secondary outcomes of ROSC, number of patients admitted to hospital, survival at 24 hours, 7 days or 28 days. The chances of being discharged alive from hospital was low in both groups; 2.5% in the cyclosporine group compared with 1.3% in the control group (P=0.23). The rates of favourable neurological outcome was similarly poor (cyclosporine, 1.8% vs control, 1.3%; P=0.59).

Study critique

This was a large trial with 6,758 patients screened and 794 patients enrolled. In contrast to many pre-hospital trials it was individual-patient randomised rather than cluster randomised.⁸⁻¹⁰ Examination of the processes of care show time to ACLS and administration of first vasopressor were similar to other pre-hospital cardiac arrest studies carried out in France.⁷ The rates of survival-to-hospital discharge are in keeping with large Utstein based registries for patients with non-shockable rhythms.¹¹ However, they were lower than the 6.6% 30 day survival seen in the PARAMEDIC trial, although this included both patients with shockable and non-shockable rhythms.⁸ Overall, these features indicate a well conducted trial. Also, there was no between-group difference in outcome in the per-protocol analysis, providing reassurance the results are robust.

It could be argued a placebo should have been given in the control arm. French investigators have previously achieved this in an OHCA trial comparing vasopressin and epinephrine, with a number of investigators named as authors in both papers.⁷ While the hospital-based physicians were blinded to group assignment, the pre-hospital physicians providing ACLS were unblinded. This may have unintentionally introduced biases; for example, by improving chest compression fraction or reducing peri-shock pauses, both of which are known to improve outcomes in OHCA.^{12,13} Although data on cardiac arrest management were collected, they were not presented in the paper.

In selecting SOFA score at 24 hours as the primary outcome measure, the authors chose a non-patient centred outcome measure. Had this trial demonstrated a between-group difference, it would have warranted a further, larger trial to look at patient centred



outcomes, which would also generate more evidence in this field and provide replication.

There are three points worthy of discussion that may explain the null result; the timing of cyclosporine, the dose of cyclosporine administered and whether any single drug intervention is likely to impact on post cardiac arrest outcome.⁶

In this trial, cyclosporine was administered at a dose of 2.5 mg/kg. This dose had shown positive results in pilot studies involving patients undergoing aortic valve surgery and undergoing percutaneous coronary interventions (PCI) for acute myocardial infarction.^{14,15} In the first of these trials, this dose was chosen arbitrarily based on the authors previous experience with cyclosporine loading in heart transplant recipients.¹⁴ However, the much larger CIRCUS trial (published after recruitment had finished in this trial) administered cyclosporine at a dose of 2.5 mg/kg to patients undergoing PCI for acute anterior ST-segment elevation myocardial infarction (STEMI) and found no difference in outcomes.¹⁶ In a number of animal models of cardiac arrest the dose used to successfully attenuate the post cardiac arrest syndrome was 5 - 10 mg/kg of cyclosporine, though this is higher than the 2-4 mg/kg used to treat inflammatory bowel disease and nephrotic syndrome.¹⁷⁻²¹

The successful pilot studies administered cyclosporine at the onset of resuscitation.^{14,15} The authors recognise that the main limitation of this trial is that cyclosporine was administered a median of 27 minutes after the onset of cardiac arrest.⁶ A typical patient had 10 minutes of untreated OHCA, followed by 9 minutes of BLS, and a further 8 minutes of ACLS prior to administration of cyclosporine and a total of 50 minutes before ROSC. Hence, the reperfusion injury may have been established prior to administration. This is in stark contrast to the TTM trial where bystander CPR was commenced a median of 1 minute into OHCA, ACLS was commenced at 10 minutes and ROSC was achieved at a median of 25 minutes. The authors point to a post hoc analysis demonstrating SOFA scores were no better in those who received cyclosporine before 29 minutes compared to those who received cyclosporine after 29 minutes (P=0.77). This demonstrates the probable futility of cyclosporine administration after the reperfusion injury has begun.

The post cardiac arrest syndrome affects multiple organ systems and is superimposed on pre-existing co-morbidities. It is also mediated through a myriad of pathways. It is worth reiterating that cyclosporine was used with the intention of reducing MPTP opening through inhibition of cyclophilin D, just one of many factors implicated in mitochondrial permeability.²⁻⁵ Temperature management has pleiotropic effects and has been one of the few strategies that has successfully ameliorated the impact of OHCA.^{6,22} The authors could not demonstrate that cyclosporine altered MPTP permeability in this human study. This process requires tissue sampling of heart, brain and liver mitochondria with subsequent electron microscopy.² On this basis, the physiological premise of the study seems ambitious.⁶ One dose of a single drug may be incapable of



stemming the inflammatory cascade causing post cardiac arrest syndrome, especially in dealing with a group of patients with a mean duration of OHCA of 50 minutes.

In summary, this was a well conducted trial reporting no difference in the primary outcome. It raises two potential areas for further work; the use of a higher cyclosporine dose and use in a cohort of patients with a shockable rhythm. The time interval between OHCA and drug delivery may have contributed to this null result, though it is unlikely this delay could be reduced in clinical practice. While cyclosporine showed initial promise, it seems improvements in outcomes from OHCA will be difficult to achieve.

Where this sits in the body of evidence

The role of cyclosporine was examined in patients with acute anterior STEMI, due to complete occlusion of the left anterior descending artery, who were undergoing primary PCI. In this phase 3, multi-centre, double-blind trial 970 patients were randomised to receive placebo or cyclosporine 2.5mg/kg prior to recanalisation. Exclusion criteria included cardiogenic shock and patients with coronary collateral vessels. A composite primary outcome measure was used consisting of death, worsening heart failure during index admission, readmission due to heart failure and adverse left ventricular remodelling. The authors predicted the primary outcome measure would occur in 49% of cases. Absent or inadequate echocardiography images in 18% of patients meant that left ventricular remodelling could not be assessed. There was no difference in the primary outcome measure between the cyclosporine treated group (59.0%) and the placebo treated group (58.1%) (OR, 1.04; 95% CI, 0.78 to 1.39; P=0.77).¹⁶

In a multi-centre, randomised controlled, phase II trial, 58 patients suffering from STEMI due to complete occlusion of the culprit artery were randomised to receive placebo or cyclosporine at a dose of 2.5mg/kg prior to PCI. The primary end point was 72 hour area under the curve (AUC) for creatine kinase and troponin I, which was felt to represent infarct size. AUC for creatine kinase was significantly reduced in the cyclosporine group (P=0.04) but there was no difference in AUC for troponin I (P=0.15). In the subgroup who underwent cardiac MRI, cyclosporine treated patients had a reduced infarct size.¹⁵

Chiari and colleagues conducted a single-centre, randomised controlled trial examining the effect of cyclosporine 2.5mg/kg administered immediately before aortic cross-clamping in 61 patients undergoing aortic valve surgery. Patients treated with cyclosporine had a significantly lower 72 hour area under the curve for troponin I (mean 155 ± 71) than those treated with placebo (mean 242 ± 225) (difference, -86.2 ± 42.5; 95% CI, -172.3 to -0.1; P=0.03).¹⁴

The TTM trial compared cooling to 33°C with 36°C in patients who had suffered an OHCA. There was no difference in mortality between the two groups; 50% in the 33°C group compared to 48% in the 36°C group (hazard ratio with a temperature of 33°C,



1.06; 95% CI, 0.89 to 1.28; P=0.51). There was no difference in rates of favourable neurological outcome.²²

Kilgannon and colleagues completed a retrospective study examining the impact of arterial oxygen levels on admission to ICU in post cardiac arrest patients. Hyperoxia was defined as PaO₂ > 300 mm Hg, normoxia 60 - 300 mm Hg and hypoxia < 60 mm Hg. 6326 patients were analysed. Mortality was highest with hyperoxia (hyperoxia group 63%, normoxia group 45%, and hypoxia group 57%). In comparison to the normoxia group, hyperoxia was associated with a higher risk of death (odds ratio, 1.8; 95% CI, 1.5 to 2.2).²³

The Carbon Control after Cardiac Arrest (CCC) trial was a small phase II trial which randomised 83 patients to targeted therapeutic mild hypercapnia (TTMH) (PaCO₂ 50 to 55 mm Hg) or targeted normocapnia (TN) (PaCO₂ 35 to 45mm Hg) during the first 24h of mechanical ventilation after cardiac arrest. The primary outcome measure was a change from baseline in serum neuron specific enolase (NSE) and S100b protein (a biomarker of glial injury). NSE increased in both groups over time, with the increase being significantly greater in the TN group than the TTMH group (P (interaction) = 0.04). There was no difference in change over time of S100b between the two groups (P (interaction) = 0.23).²⁴

Should we use cyclosporine in the management of out-of-hospital cardiac arrest?

No. On the basis of this trial, there is no benefit from cyclosporine in cardiac arrest.



References

1. Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Böttiger BW, et al. Post-Cardiac Arrest Syndrome. *Circulation*. 2008 Dec 2;118(23):2452–83.
2. Baines CP, Kaiser RA, Purcell NH, Blair NS, Osinska H, Hambleton MA, et al. Loss of cyclophilin D reveals a critical role for mitochondrial permeability transition in cell death. *Nature*. 2005 Mar 31;434(7033):658–62.
3. Petronilli V, Cola C, Bernardi P. Modulation of the mitochondrial cyclosporine A-sensitive permeability transition pore. II. The minimal requirements for pore induction underscore a key role for transmembrane electrical potential, matrix pH, and matrix Ca²⁺. *J Biol Chem*. 1993 Jan 15;268(2):1011–6.
4. Halestrap AP, Richardson AP. The mitochondrial permeability transition: a current perspective on its identity and role in ischaemia/reperfusion injury. *J Mol Cell Cardiol*. 2015 Jan;78:129–41.
5. Halestrap AP, Clarke SJ, Javadov SA. Mitochondrial permeability transition pore opening during myocardial reperfusion—a target for cardioprotection. *Cardiovasc Res*. 2004 Feb 15;61(3):372–85.
6. Becker LB, Berger PB. cyclosporine for Reperfusion Injury After Cardiac Arrest: Too Little Too Late? *JAMA Cardiol*. 2016 Aug 1;1(5):566–7.
7. Gueugniaud P-Y, David J-S, Chanzy E, Hubert H, Dubien P-Y, Mauriau-court P, et al. Vasopressin and Epinephrine vs Epinephrine Alone in Cardiopulmonary Resuscitation. *New England Journal of Medicine*. 2008 Jul 3;359(1):21–30.
8. Perkins GD, Lall R, Quinn T, Deakin CD, Cooke MW, Horton J, et al. Mechanical versus manual chest compression for out-of-hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial. *The Lancet*. 2015 Mar;385(9972):947–55.
9. Austin MA, Wills KE, Blizzard L, Walters EH, Wood-Baker R. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in pre-hospital setting: randomised controlled trial. *BMJ*. 2010 Oct 18;341:c5462.
10. Hostler D, Everson-Stewart S, Rea TD, Stiell IG, Callaway CW, Kudenchuk PJ, et al. Effect of real-time feedback during cardiopulmonary resuscitation outside hospital: prospective, cluster-randomised trial. *BMJ*. 2011 Feb 4;342:d512.
11. Hasselqvist-Ax I, Riva G, Herlitz J, Rosenqvist M, Hollenberg J, Nordberg P, et al. Early Cardiopulmonary Resuscitation in Out-of-Hospital Cardiac Arrest. *New England Journal of Medicine*. 2015 Jun 11;372(24):2307–15.
12. Rea T, Olsufka M, Yin L, Maynard C, Cobb L. The relationship between chest compression fraction and outcome from ventricular fibrillation arrests in prolonged resuscitations. *Resuscitation*. 2014 Jul 1;85(7):879–84.
13. Cheskes S, Schmicker RH, Verbeek PR, Salcido DD, Brown SP, Brooks S, et al. The



- impact of peri-shock pause on survival from out-of-hospital shockable cardiac arrest during the Resuscitation Outcomes Consortium PRIMED trial. *Resuscitation*. 2014 Mar 1;85(3):336–42.
14. Chiari P, Angoulvant D, Mewton N, Desebbe O, Obadia J-F, Robin J, et al. cyclosporine protects the heart during aortic valve surgery. *Anesthesiology*. 2014 Aug;121(2):232–8.
 15. Piot C, Croisille P, Staat P, Thibault H, Rioufol G, Mewton N, et al. Effect of cyclosporine on reperfusion injury in acute myocardial infarction. *N Engl J Med*. 2008 Jul 31;359(5):473–81.
 16. Cung T-T, Morel O, Cayla G, Rioufol G, Garcia-Dorado D, Angoulvant D, et al. cyclosporine before PCI in Patients with Acute Myocardial Infarction. *New England Journal of Medicine*. 2015 Sep 10;373(11):1021–31.
 17. Huang C-H, Tsai M-S, Hsu C-Y, Su Y-J, Wang T, et al. Post-cardiac arrest myocardial dysfunction is improved with cyclosporine treatment at onset of resuscitation but not in the reperfusion phase. *Resuscitation*. 2011;82 Suppl 2:S41–7.
 18. Cour M, Abrial M, Jahandiez V, Loufouat J, Belaïdi E, Gharib A, et al. Ubiquitous protective effects of cyclosporine A in preventing cardiac arrest-induced multiple organ failure. *J Appl Physiol*. 2014 Oct 15;117(8):930–6.
 19. Gill RS, Lee T-F, Manouchehri N, Liu J-Q, Lopaschuk G, Bigam DL, et al. Postresuscitation cyclosporine treatment attenuates myocardial and cardiac mitochondrial injury in newborn piglets with asphyxia-reoxygenation. *Crit Care Med*. 2013 Apr;41(4):1069–74.
 20. Van Assche G, D’Haens G, Noman M, Vermeire S, Hiele M, Asnong K, et al. randomised, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology*. 2003;125(4):1025–31.
 21. Salomon R, Gagnadoux M-F, Niaudet P. Intravenous cyclosporine therapy in recurrent nephrotic syndrome after renal transplantation in children. *Transplantation*. 2003 Mar 27;75(6):810–4.
 22. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest. *New England Journal of Medicine*. 2013 Dec 5;369(23):2197–206.
 23. Kilgannon J, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA*. 2010 Jun 2;303(21):2165–71.
 24. Eastwood GM, Schneider AG, Suzuki S, Peck L, Young H, Tanaka A, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: A phase II multi-centre randomised controlled trial (the CCC trial). *Resuscitation*. 2016 Jul;104:83–90.



Eastwood GM, Schneider AG, Suzuki S, Peck L, Young H, Tanaka A, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: A phase II multi-centre randomised controlled trial (CCC trial). Resuscitation 2016;104:83–90

Introduction

During cardiac arrest (CA), the brain undergoes changes in cerebral blood flow (CBF). Much of the knowledge surrounding the four characteristic phases of cerebral blood flow at this time are derived from animal models.¹ In untreated cardiac arrest, there is a period of multifocal no-reflow (phase I); cardiopulmonary resuscitation (CPR) then creates global hyperaemia (phase II). In the first 24 hours after return of spontaneous circulation (ROSC), there is delayed hypoperfusion (phase III), and as cerebral metabolic rate may not demonstrate a commensurate reduction, relative ischaemia ensues. Finally in phase IV, low, normal or increased CBF may be seen.¹

The complex interplay in CBF, intra-cranial pressure (ICP) and cerebral metabolic rate is poorly understood. Studies using Xenon-133 to measure CBF after CA showed non-survivors had a higher CBF than survivors ($P < 0.01$), with the peak CBF typically occurring 18 to 30 hours following CA.² Transcranial doppler studies of the middle cerebral artery reveal cerebral autoregulation is often lost during the post cardiac arrest period. In those with preserved autoregulation, there is a “rightward shift”, with autoregulation lost below mean arterial pressures of 80 to 120 mm Hg.³ Finally, intra-cranial hypertension > 25 mm Hg is associated with death or severe disability following CA.⁴

The effect of PaCO₂ on CBF has recently come under scrutiny. Observational studies demonstrate hypercapnia following CA to be an independent predictor of good neurological outcome, with hypocapnia being associated with poor neurological outcome.^{5,6} To date, this has not been tested in a clinical randomised controlled trial.

Study synopsis

The Carbon Control after Cardiac Arrest (CCC) trial was a phase II safety and feasibility, multi-centre, randomised controlled trial of targeted therapeutic mild hypercapnia (TTMH) after CA. The authors hypothesised that biomarkers of neuronal and glial injury may provide evidence of either benefit or harm from 24 hours of TTMH following CA.

Patients aged ≥ 18 years who required mechanical ventilation following non-traumatic in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) were eligible for inclusion. Exclusion criteria included imminent death, evidence of raised intra-cranial pressure or intra-cranial haemorrhage, pregnancy, severe airflow limitation, and metabolic acidosis ($\text{pH} < 7.1$ and base excess < -6 mmol/L) which could not be corrected within the first two hours of ICU admission.



Patients were randomised on a 1:1 basis using permuted blocks of 2 to 6. Patients were randomly allocated to receive either targeted normocapnia (TN) (PaCO₂ 35 to 45 mm Hg / 4.7 to 6.0 kPa) or TTMH (PaCO₂ 50 to 55mm Hg / 6.7 to 7.3 kPa) during the first 24 hours of mechanical ventilation. The target PaCO₂ could be achieved by varying respiratory rate, tidal volume or both. Beyond 24 hours, the target PaCO₂ was at the discretion of the treating clinicians. All other aspects of post-arrest management were at the discretion of the treating clinician.

The primary outcome measure was the change from baseline in serum neuron specific enolase (NSE) (a biomarker of neuronal injury) and S100b protein (a biomarker of glial injury). Biomarkers were measured at baseline, 24h, 48h and 72h after randomisation. Secondary outcome measures included mortality, ICU and hospital length of stay, and functional status at 6 months (assessed using Glasgow Outcome Scale Extended (GOSE), an 8 point scale with scores ≥ 5 indicating a favourable neurological outcome) and discharge destination. A number of feasibility and safety outcomes were also recorded (including episodes of overt raised intra-cranial pressure).

As a feasibility study no formal power calculation was undertaken, but a target sample size of 50 patients surviving to 72 hours with full serum biomarker measurements was aimed for. Due to the appreciable mortality in the post cardiac arrest period, more than 50 patients would need to be recruited to achieve the desired sample size. A modified intention-to-treat (ITT) analysis was performed. A two-sided p-value of 0.05 was chosen to indicate statistical significance.

187 patients were screened and 86 enrolled. The main reasons for exclusion were imminent withdrawal of treatment (n = 31), metabolic acidosis (n = 28), spontaneous ventilation (n = 20), suspected raised intra-cranial pressure (n = 14), and intra-hospital transfer (n = 2). Three patients withdrew consent leaving 83 patients in the ITT analysis. Twenty-one patients were discharged alive from ICU before 72 hours, 6 patients died and 3 patients had an incomplete set of biomarkers. Fifty patients were alive with a full set of biomarkers at 72 hours.

Of the initial 83 patients, 42 patients were allocated to TTMH group and 41 to the TN group. The baseline characteristics of the groups were well balanced in relation to patient demographics, cardiac arrest characteristics and post cardiac arrest management. 81% had an OHCA. Ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) was the presenting rhythm in 71% of cases. The mean time to return of spontaneous circulation was 17 minutes. 68% of patients received bystander CPR. Patients received on average 64 hours of mechanical ventilation. The median time from cardiac arrest to enrolment was 252 minutes.

There was good separation between the groups in relation to median (IQR) PaCO₂ levels

during the first 24 hours; 41 mm Hg (38 to 42 mm Hg) vs 49 mm Hg (44 to 52 mm Hg) in the TN and TTMH groups, respectively ($P < 0.001$). Of the patients in the TN group, 90% had a mean PaCO_2 in the normocapnic range (35 to 45 mm Hg), compared to 19% of the TTMH group ($P < 0.001$). In comparison, patients in the TTMH group were more likely to have a mean PaCO_2 in the target TTMH range of 50 to 55 mm Hg (38% vs 0%; $P < 0.001$) or in the PaCO_2 range between 45 and 50 mm Hg (31% vs 5%; $P = 0.01$). No patients had severe hypercapnia > 70 mm Hg. However, more patients suffered hypocapnia in the TN group; 20% of all arterial blood gas measurements compared to 8% ($P < 0.001$).

During the first 24 hours, both minute ventilation ($P < 0.001$) and respiratory rate ($P < 0.001$) were lower in the TTMH group. No data was presented on tidal volume. There was no difference in the mean pH during the first 24 hours ($P = 0.90$). There were no differences in relation to PaO_2 levels, rates of cooling, body temperature or blood glucose levels during the first 24 hours.

NSE increased in both groups over time, with the increase being significantly greater in the TN group than the TTMH group (P (interaction) = 0.04). The TTMH group demonstrated a decrease in S100b with time, while the TN group demonstrated no change. However, there was no statistically significant difference in change over time of S100b between the two groups (P (interaction) = 0.23). There was 94% followup at 6 months; 59% of the TTMH group had a favourable neurological outcome compared to 46% of the TN group ($P = 0.26$). There was no significant difference in ICU or hospital length of stay or mortality. No patients were identified as having overt raised intracranial pressure.

Study critique

This interesting phase II feasibility study is the first randomised controlled trial to examine the effect of TTMH on biomarkers of neurological injury and patient outcomes following cardiac arrest. As a phase II trial its results are designed to inform the conduct of further research and are not intended to change clinical practice. It was a well conducted study with patients being enrolled, on average, just 4 hours following their cardiac arrest. Patients were recruited at a rate of 0.8 per week across four centres. By including both IHCA and OHCA patients with any presenting rhythm, the ratio of those screened to those recruited was 2.2:1. Only 6 eligible patients were missed. Good separation was achieved in PaCO_2 between the groups demonstrating internal validity. The changes in NSE levels point towards a potential patient benefit. There was no signal of harm in the safety outcomes, which were conducted on an ITT population, not just the 50 patients alive with complete biomarkers at 72 hours. These results suggest it would be both safe and feasible to conduct a larger phase III study.

The authors included non-traumatic IHCA and OHCA in an effort to improve generalisability. However, the inclusion and exclusion criteria meant some of the sickest



patients were excluded, such as patients not expected to survive, those with suspected raised ICP, severe COPD and severe metabolic acidosis. As a consequence, the patients recruited often had cardiac arrest characteristics predictive of good neurological outcomes, namely VF/VT as an initial presenting rhythm (71%), bystander CPR (68%) and in-hospital cardiac arrest (19%).⁷⁻⁹ Overall, 69% of patients survived to hospital discharge. Therefore, the patients recruited into this study are not representative of cardiac arrest patients seen in both IHCA and OHCA registries.⁷⁻⁹ However, the mortality seen in the TTM trial was not dissimilar, at 51%.¹⁰ This feature should be borne in mind in designing further studies or interpreting the results of these studies.

One potential confounding variable is the high rate of hypocapnia in the TN control group (20% vs 8%; $P < 0.001$). In a retrospective, observational study of 16,542 patients admitted to ICU following cardiac arrest, hypocapnia was associated with an increase in mortality in comparison to normocapnia (OR, 1.12; 95% CI, 1.00 to 1.24; $P = 0.04$).⁵ It is possible that the harmful effects of hypocapnia in the control group account for some of the outcome differences observed.

The pragmatic trial design meant other aspects of cardiac arrest management were at the discretion of the treating clinician. These were well balanced between the two groups leading the authors to suggest “lack of blinding did not affect the process of care and is unlikely to account for the difference in biomarker concentrations”. However, in the first 24 hours the TTMH group received higher doses of midazolam (57mg vs 23mg) and morphine (77mg vs 56mg) and were more likely to receive neuromuscular blockade (52% vs 39%). Although none of these features reached statistical significance in this small trial, it potentially points towards higher doses of sedation to limit minute ventilation. Prospective observational data demonstrates sedation in the 12 hours prior to measurement of NSE reduces the sensitivity and specificity of NSE to predict poor neurological outcomes at three months.¹¹ Thus, the use of sedation to achieve a targeted PaCO_2 is a potential confounding variable when looking at trends in NSE.

Furthermore, in a porcine model of cardiac arrest, a reduction in ventilation frequency during resuscitation resulted in improved coronary perfusion pressure (10.1 ± 4.5 mm Hg vs 19.3 ± 3.2 mm Hg, $P = 0.007$) and cerebral perfusion pressure (7.7 ± 6.2 mm Hg versus 14.5 ± 5.5 mm Hg, $P = 0.008$).¹² The respiratory rates used in the TTMH group were significantly lower than those in the TN group. If this pattern were to continue in a phase III trial, it may be difficult to ascertain whether TTMH, ventilation strategy or sedation is responsible in outcome differences.

In this study, the authors hypothesised that biomarkers of neuronal and glial injury may provide evidence of either benefit or harm from TTMH. This seems a pragmatic choice in a feasibility study. Biomarkers have been examined in a number of observational studies looking at conditions such as cardiac arrest, stroke and following cardiac surgery.^{11,13-15} A



study by Shinozaki and colleagues of 80 patients who suffered non-traumatic cardiac arrest, demonstrated that S100b levels of greater than 0.05 ng/ml at 24 hours had an area under the ROC curve of 1.0 in predicting a poor neurological outcomes.¹⁶ However, other studies have been less compelling and have found clinical examination to be more sensitive and specific.^{11,17} As with any test, the population in which biomarkers are used may influence their sensitivity and specificity. In the previously mentioned study by Shinozaki and colleagues, 83.8% of patients had a poor neurological outcome at 6 months (cerebral performance category 3 to 5).¹⁶ In contrast, only 48.8% of patients in the TTM trial had a poor neurological outcome at 6 months.⁴ Rates of good neurological outcome were even higher in the TTMH group in the CCC trial, this could offer some explanation for the poor performance of biomarker S100b.

Overall this trial has demonstrated that TTMH is both safe and feasible. Based upon this pilot study and other supporting evidence, the authors are in the process of developing the TAME Cardiac Arrest trial, which plans to recruit 1700 patients. This aims to be an international, multi-centre, randomised, controlled trial which will determine whether targeted TTMH (PaCO₂ 50 to 55 mm Hg) improves neurological outcome at 6 months compared to standard care (targeted normocapnia; PaCO₂ 35 to 45 mm Hg) in resuscitated cardiac arrest patients admitted to the ICU. The investigators also plan to further evaluate NSE, but not S100b, in a nested cohort study as part of the TAME trial (*personal communication with Dr Glenn Eastwood, Melbourne, Australia*).

Where this sits in the body of evidence

The effect on outcomes of PaCO₂ in the first 24 hours following cardiac arrest was examined in an observational study of 16,542 consecutive patients admitted to ICU in Australia and New Zealand. PaCO₂ levels were taken from arterial blood gases (ABG) using the APACHE methodology i.e. for patients on an FiO₂ ≥ 0.5 the ABG with the highest alveolar-arterial gradient was selected; for patients with FiO₂ < 0.5 the ABG with the lowest PaO₂ was selected. After adjustment for confounding variables, patients with hypocapnia (PaCO₂ < 35 mm Hg) had a higher mortality than those with normocapnia (PaCO₂ of 35 to 45 mm Hg) (OR, 1.12; 95% CI, 1.00 to 1.24; P=0.04). Mortality did not differ between patients with normocapnia or hypercapnia (PaCO₂ > 45 mm Hg) (P=0.13).

The FINNRESUSCI study was a prospective observational study examining the effect of mean PaCO₂ during the first 24 hours on neurological outcomes at one year following OHCA. In this study of 409 patients, the mean PaCO₂ was an independent predictor of good neurological outcome at one year (OR for an increase of 1 mm Hg, 1.054; 95% CI, 1.006 to 1.104; P=0.027). In contrast mean PaO₂ was not (OR, 1.006; 95% CI, 0.998 to 1.014; P=0.149).⁶

A retrospective study of 6326 patients admitted to ICU following CA examined the impact of oxygenation on outcomes. Patients with hyperoxia (PaO₂ of ≥ 300 mm Hg) on



their first ABG had a higher mortality (63%) than those with normoxia (45%) or those with hypoxia ($\text{PaO}_2 < 60\text{mm Hg}$ or $\text{PaO}_2/\text{FiO}_2$ ratio < 300 mm Hg) (57%). Following multiple logistic regression analysis exposure to hyperoxia was a predictor of in-hospital mortality (OR, 1.8; 95% CI, 1.5 to 2.2; $P < 0.001$). Exposure to hypoxia was also a predictor of in-hospital mortality (OR, 1.3; 95% CI, 1.1 to 1.5; $P = 0.009$).¹⁸

Cronberg and colleagues completed a prospective, observational study of 111 ICU patients who had suffered a CA and were treated with hypothermia. NSE was measured in a subgroup of 34 patients still comatose at 72 hours. Of the 17 patients with NSE levels > 33 ng/ml, all failed to regain consciousness and subsequently died; this correlated with changes consistent with brain injury on MRI, somatosensory evoked potentials or autopsy. In contrast, of the 17 patients with NSE levels < 33 ng/ml, 6 regained consciousness.¹³

In a prospective observational study involving 85 patients who had suffered CA, the role of NSE in predicting death or vegetative at three months was assessed. NSE levels > 33 ng/ml at 72 hours had a sensitivity of 77% (95% CI, 61% to 88%) and a specificity of 81% (95% CI, 60% to 93%). It was less specific than absence of somatosensory evoked potentials, absent pupillary response, absent corneal reflex or motor response ≤ 2 . The use of sedation in the 12 hours prior to measurement of NSE further reduced sensitivity and specificity.¹¹

In 44 patients who suffered an acute ischaemic stroke, the correlation between neurobiomarkers and infarct size and clinical outcomes were examined. Peak S100 levels correlated with infarct volume on CT brain at day 4 ($r = 0.75$, $P < 0.001$) and with Glasgow Outcome Scale score ($r = 0.51$, $P < 0.001$). However, peak NSE levels correlated less well with infarct volume ($r = 0.37$, $P < 0.05$) and did not correlate with clinical outcome ($r = 0.18$, $P > 0.05$).¹⁴

Should we implement this into our practice?

No. We should await a large phase III study.

References

1. Buunk G, van der Hoeven JG, Meinders AE. Cerebral blood flow after cardiac arrest. *The Netherlands Journal of Medicine*. 2000 Sep;57(3):106–12.
2. Cohan SL, Mun SK, Petite J, Correia J, Silva ATTD, Waldhorn RE. Cerebral blood flow in humans following resuscitation from cardiac arrest. *Stroke*. 1989 Jun 1;20(6):761–5.
3. Sundgreen C, Larsen FS, Herzog TM, Knudsen GM, Boesgaard S, Aldershvile J. Autoregulation of Cerebral Blood Flow in Patients Resuscitated From Cardiac Arrest. *Stroke*. 2001 Jan 1;32(1):128–32.
4. Gueugniaud P-Y, Garcia-Darenes F, Gaussorgues P, Bancalari G, Petit P, Robert D. Prognostic significance of early intra-cranial and cerebral perfusion pressures in post-cardiac arrest anoxic coma. *Intensive Care Med*. 1991 Jul 1;17(7):392–8.
5. Schneider AG, Eastwood GM, Bellomo R, Bailey M, Lipcsey M, Pilcher D, et al. Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. *Resuscitation*. 2013 Jul;84(7):927–34.
6. Vaahersalo J, Bendel S, Reinikainen M, Kurola J, Tiainen M, Raj R, et al. Arterial Blood Gas Tensions After Resuscitation From Out-of-Hospital Cardiac Arrest: Associations With Long-Term Neurologic Outcome. *Critical Care Medicine*. 2014 Jun;42(6):1463–70.
7. Hasselqvist-Ax I, Riva G, Herlitz J, Rosenqvist M, Hollenberg J, Nordberg P, et al. Early Cardiopulmonary Resuscitation in Out-of-Hospital Cardiac Arrest. *New England Journal of Medicine*. 2015 Jun 11;372(24):2307–15.
8. Wissenberg M, Lippert FK, Folke F, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. *JAMA*. 2013 Oct 2;310(13):1377–84.
9. Meaney PA, Nadkarni VM, Kern KB, Indik JH, Halperin HR, Berg RA. Rhythms and outcomes of adult in-hospital cardiac arrest: *Critical Care Medicine*. 2010 Jan;38(1):101–8.
10. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med*. 2013 Dec 5;369(23):2197–206.
11. Samaniego EA, Mlynash M, Caulfield AF, Eyingorn I, Wijman CAC. Sedation Confounds Outcome Prediction in Cardiac Arrest Survivors Treated with Hypothermia. *Neurocrit Care*. 2010 Aug 3;15(1):113–9.
12. Yannopoulos D, McKnite SH, Tang W, Zook M, Roussos C, Aufderheide TP, et al. Reducing Ventilation Frequency During Cardiopulmonary Resuscitation in a Porcine Model of Cardiac Arrest. *Respiratory Care*. 2005 May 1;50(5):628–35.



13. Cronberg T, Rundgren M, Westhall E, Englund E, Siemund R, Rosén I, et al. Neuron-specific enolase correlates with other prognostic markers after cardiac arrest. *Neurology*. 2011 Aug 16;77(7):623–30.
14. Missler U, Wiesmann M, Friedrich C, Kaps M. S-100 protein and neuron-specific enolase concentrations in blood as indicators of infarction volume and prognosis in acute ischemic stroke. *Stroke*. 1997 Oct;28(10):1956–60.
15. Georgiadis D, Berger A, Kowatschev E, Lautenschläger C, Börner A, Lindner A, et al. Predictive value of S-100beta and neuron-specific enolase serum levels for adverse neurologic outcome after cardiac surgery. *J Thorac Cardiovasc Surg*. 2000 Jan;119(1):138–47.
16. Shinozaki K, Oda S, Sadahiro T, Nakamura M, Abe R, Nakada T, et al. Serum S-100B is superior to neuron-specific enolase as an early prognostic biomarker for neurological outcome following cardiopulmonary resuscitation. *Resuscitation*. 2009 Aug 1;80(8):870–5.
17. Zellner T, Gärtner R, Schopohl J, Angstwurm M. NSE and S-100B are not sufficiently predictive of neurologic outcome after therapeutic hypothermia for cardiac arrest. *Resuscitation*. 2013 Oct;84(10):1382–6.
18. Kilgannon J, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA*. 2010 Jun 2;303(21):2165–71.



Respiratory Trials



High-Flow Nasal Oxygen vs Facemask Oxygen post-extubation

Hernández G, Vaquero C, González P, Subira C, Frutos-Vivar F, Rialpet G al.
Effect of post-extubation High-Flow Nasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients - A randomised Clinical Trial.
JAMA 2016;315(13):1354-61

Introduction

Mechanical ventilation is a life-saving intervention for critically ill patients. However, prolonged ventilation is associated with complications such as ventilator-induced lung injury, ventilator-associated pneumonia and increased length of intensive care and hospital stay. Timely extubation is therefore a clinical priority. Liberation from ventilation is dependent on several factors, including the resolution of the original condition necessitating ventilation, an acceptable level of consciousness, and adequate return of respiratory function with the ability to clear secretions. Despite considerable investigative effort, predictors of weaning success lack sensitivity and specificity.^{1,2} Furthermore, despite weaning guidelines³, extubation still results in failure in 10 to 20% of attempts.⁴⁻⁸ Reintubation is associated with prolonged ventilation, increased organ dysfunction and increased mortality rates.^{4,6-8} Although requirement for reintubation and increased mortality could reflect underlying illness, after adjustment for coexisting conditions and severity of illness, extubation failure is still an independent predictor of death.⁹ Prevention of reintubation and reduction of the work of breathing in the post-extubation period may therefore have beneficial effects on outcome. As such, non-invasive ventilation (NIV) has been investigated for the prevention of reintubation and as a bridge to conventional oxygen therapy.

A recent meta-analysis suggested NIV may be beneficial particularly in patients with a history of chronic obstructive airway disease.¹⁰ However, NIV is not always tolerated. High-flow nasal oxygen (HFNO) has been used as an alternative means of respiratory support. HFNO reduces anatomical dead space,¹¹ provides stable inspired oxygen concentrations¹² and may increase lung volumes by generating low levels of positive end expiratory pressure.¹³ In a recent study of acute hypoxic respiratory failure patients, HFNO compared favourably with NIV. HFNO has also shown benefit in a further small study of general intensive care patients after extubation.¹⁴ This effect may have reflected a benefit in lower risk patients, further study of high-flow in lower risk patients is therefore both timely and justified.

Study synopsis

This was a open label, multi-centre, randomised trial performed in seven ICUs in Spain. The study aimed to investigate the effect of HFNO versus conventional oxygen therapy for preventing reintubation in mechanically ventilated patients. Adult patients were eligible if they were ventilated in ICU for between twelve hours and seven days,



tolerated a spontaneous breathing trial and were considered low risk for reintubation. Patients were defined as low risk if they were less than 65 years old, had an APACHE II score less than twelve on the day of extubation, had a body mass index less than 30 kg/m², were not ventilated due to heart failure, did not have moderate to severe COPD, or more than two predefined co-morbidities and were able to adequately manage respiratory secretions. Exclusion criteria included a do-not-resuscitate order, tracheostomy or unplanned extubation. Patients who were hypercapnic during the spontaneous breathing trial were also excluded.

Randomisation was performed with a random-number generator in blocks of ten through a telephone call center and was stratified for centre. Patients were allocated to HFNO or conventional oxygen therapy. HFNO was commenced immediately following extubation, with an initial flow of 10 L/min, which was increased until the patient reported discomfort. Temperature was set at 37 °C and FiO₂ titrated to maintain oxygen saturations above 92%. After 24 hours conventional oxygen delivery was instituted. In the conventional oxygen therapy group saturations were similarly targeted.

The primary outcome was reintubation within 72 hours after extubation. There were predefined criteria for immediate and late (up to 72 hours) reintubation. The main secondary outcomes were post-extubation respiratory failure and respiratory infection. Data was also collected on sepsis, multiorgan failure, ICU and hospital length of stay and mortality, time to reintubation, and adverse effects. Assuming a reintubation rate of 13%, a total sample size of 520 patients was calculated to have 80% power to detect an absolute reduction of 8% in favour of HFNO at a 2-sided 5% significance level, and a maximum tolerated patient loss rate of 15%.

1,739 patients receiving mechanical ventilation for longer than 12 hours were identified with 527 (30%) randomised: 264 to the high-flow group and 263 to the conventional group. The majority of exclusions were due to a high risk for reintubation (54%), with hypercapnia during a spontaneous breathing trial the next most common exclusion (7%). Groups were similar at baseline with the exception of neurological disease, which was more common in the conventional oxygen group (12.9% vs 7.8%). Randomised patients were approximately 51 years of age, with a mean APACHE score around 14 on admission. They had a mixture of medical and surgical conditions: primary respiratory failure (16.5%), neurological pathology (29.4%), trauma (15.7%) and post-operative (47.6%). Prior to attempted extubation, patients had been ventilated for between 1 to 2 days.

At 12 hours post-extubation, the HFNO group were receiving a slightly lower mean (SD) FiO₂, 0.32 (0.08) vs 0.4 (0.09); difference -0.08; 95% CI, -0.09 to -0.07; P<0.001. The HFNO group mean flow rate at this time was 30.9 (7.6) L/min. There was no difference in PaO₂/FiO₂, PaCO₂ or pH.



Overall, reintubation within 72 hours was lower in the high-flow group: 13 patients (4.9%) vs 32 patients (12.2%) in the conventional group (difference, 7.2%; 95% CI, 2.5% to 12.2%; $P=0.004$). Nine patients in both groups required reintubation for non-respiratory reasons (surgery/low GCS); therefore, the reintubation reduction was mainly attributable to a lower incidence of respiratory-related reintubation in the high-flow group: 1.5% vs 8.7% (difference, 7.2%; 95% CI, 3.6% to 11.4%; $P=0.001$). The number needed to treat with high-flow was 14 patients to prevent one reintubation. There were seven patients in the conventional group reintubated due to laryngeal oedema compared to none in the high-flow group. When the primary outcome was re-analysed after excluding patients requiring re-intubation for laryngeal oedema, there was still a significant reduction in re-intubation rates, 4.9% vs 9.8%, $P=0.04$.

In terms of secondary outcomes, the most significant finding was a lower rate of post-extubation respiratory failure in the high-flow group: 8.3% vs 14.4%; difference, 6.1%; 95% CI, 0.7% to 11.6%; $P=0.03$. The most common reasons for respiratory failure (HFNO vs control) were an inability to clear secretions 13.6% vs 36.8%; hypoxia, 31.8% vs 15.8%; and unbearable dyspnoea, 40.9% vs 28.9%. There were no differences in ICU mortality: 1.1% vs 1.1%, $P=0.99$; hospital mortality 3.8% vs 5%, $p=0.94$; or respiratory infections 2.3% vs 4.9%, $P=0.07$.

There was no difference in median (IQR) time to reintubation between groups; HFNO group 19 (12-28) hours vs conventional oxygen group 15 (9-31) hours; absolute difference, -4; 95% CI, -54 to 46; $P=0.66$. No adverse effects were reported.

Study critique

Extubation after invasive ventilation is associated with increased work of breathing.¹⁵ Although conventional oxygen supplementation may help prevent hypoxia, low-flow oxygen via a face mask or nasal cannula does not provide additional respiratory support. HFNO has been shown to improve oxygenation and reduce respiratory rates in patients with respiratory failure.¹⁶ The hypothesis of the trial was that high-flow nasal oxygen, by providing enhanced respiratory support, would reduce patient requirement for reintubation. Therefore, this trial both has a sound theoretical physiological basis and addresses an important clinical problem.

This study is the largest yet comparing HFNO with standard oxygen therapy for the prevention of post-extubation failure. There were many strengths in the methodology, design and conduct of the study, not least there were no dropouts in the entire trial. Predefined criteria for selection of lower risk patients were used. There was also clear criteria for the indications for initiation of a weaning trial, and most importantly, comprehensive definition of failure. Overall, this ensured extubated patients had fulfilled a repeatable standardised assessment of readiness for extubation. A robust randomisation process, with stratification by site, was used, which will have assisted in



eliminating inter-hospital differences in extubation failure rates. There were also reintubation criteria, albeit with clinician discretion, which ensured patients in both groups were reintubated for the same indications. Finally, although blinding is not possible in such a trial, the investigators were separate from the clinical team, and the statistical analysis was performed in a blinded fashion, increasing confidence in the reported results.

Some aspects of the trial should be considered before treating all extubated patients with HFNO. Firstly, the patient population studied. Recommended criteria for readiness to wean¹⁷ were used and patients were screened daily. This potentially reduces the time between when clinical suspicion arises that weaning is possible and the beginning of actual assessment. However, using these criteria, 83% of screened patients were excluded. Although the criteria defines a stable intensive care patient, perhaps they were too stable. Patients who do not fulfil these criteria may still be able to wean successfully, and therefore the criteria should be viewed as considerations for probable weaning rather than as strict criteria that must all be met. The study therefore, could have delayed extubation attempts for some patients.

Criteria were also used for identifying high risk patients for extubation failure, which excluded a further 54%. However, criteria defining high risk is difficult to standardise. Although multiple studies⁴⁻⁸ have identified associations with increased risk, in reality there is probably a complex interplay between the presence and severity of a risk factor and the patient's critical illness. The inclusion criteria resulted in almost half the patients being post-operative, having a low severity of illness scores or only requiring ventilation for a short period of time. The reported rates of reintubation in the control group may seem relatively high in this light.

Despite a robust stratified randomisation process, there were some differences in the assigned groups. The conventional group had a higher proportion of patients with neurological conditions (32.7% vs 26.1%), mainly intra-cranial and subarachnoid haemorrhage, a set of pathologies which have been independently associated with a greater risk of extubation failure.⁵ Neurological impairment, particularly with a poor cough, is associated with extubation failure.^{18,19} Conversely, the HFNO group had more patients with traumatic brain injury (11.7% vs 6.5%), although there may not be a correlation between Glasgow Coma Scale (GCS) scores and reintubation.²⁰ As patients had to be able to spontaneously cough, and were mostly extubated after one day, presumably neurological injury was not too severe. There were also greater rates of medical conditions (74.5% vs 66.3%) and acute respiratory distress syndrome (4.2% vs 1.5%) in the conventional group. Medical patients have been associated with worse outcomes.⁷ Whilst some of these differences are small, and only the neurological admission difference was significant, this trial had a fragility index of just five patients.



Given this fragility index and the relatively low incidence of reintubations in the study population, as in other studies, the decision to reintubate and the criteria for such a decision are extremely important. The study defined immediate reintubation criteria as either respiratory (which included primary respiratory failure and also other problems such as haemodynamic instability, agitation and symptomatic bradycardias which may not be related to respiratory failure) and others which were mainly either surgery related or due to a decreased level of consciousness. A potential issue with this classification is the assumption that multiple pathologies can be categorised simplistically under respiratory causes and that the intervention which primarily supports the respiratory system could influence non respiratory pathologies. In reality, there were few immediate reintubations in each group, and the number of intubations related to non-respiratory causes were identical. The main reason for reintubation was persistent post-extubation respiratory failure. This was again defined, but it is arguable the criteria were less clear and perhaps open to interpretation. The reintubation criteria were not validated. In addition, they may not reflect current practice; for instance, a patient who had desaturated on an FiO_2 of 0.5 could be reintubated.

The main causes for persistent respiratory failure were unbearable dyspnoea in both groups, secretion retention in the conventional group and perhaps surprisingly, hypoxia in the high-flow group. It was interesting that only 9% of the high-flow group with post-extubation respiratory failure were reintubated while 42% of the conventional oxygen group were deemed to require reintubation by the treating physicians. The beneficial effect of HFNO over conventional oxygen therapy in prevention of intubation in a trial of acute respiratory failure was less significant.²¹ Perhaps the seemingly dramatic reduction in reintubation rate could have been influenced by the non blinded clinician content to persist with HFNO, while less content to persist with conventional oxygen therapy.

The trialists provide various reasons why HFNO may have potentially reduced respiratory failure and respiratory related reintubations. Firstly, by a reduction in hypoxia. While both groups had similar numbers of hypoxic patients, and the HFNO group had a greater percentage of patients with hypoxia as the cause of respiratory failure, more of the conventional group required intubation. By providing PEEP, HFNO may improve oxygenation. However the levels of PEEP are low generally less than 3 cmH_2O , are dependent on flow rates and vary considerably.^{12,13} Despite low levels of PEEP in post-operative cardiac surgery patients, HFNO has been shown to increase lung volumes, with lung expansion proportional to flow rates.²² However, the flow rates in the intervention group reported at 12 hours were only 30 L/min. This level of flow probably produces less than 1 cmH_2O of PEEP and was below the level of flow commenced in the lung expansion study. The effect of this level of support is therefore questionable. At 12 hours the HFNO group did require less inspired oxygen. High-flow has been shown to provide stable inspiratory oxygen concentrations, which may reduce with exercise.¹² In comparison, the oxygen concentration provided by low flow devices is variable, and can



be lower than prescribed and decrease with increasing respiratory distress.²³ It is therefore unclear if the difference in inspired oxygen was indeed significant.

A further proposed mechanism was the effect on work of breathing and respiratory muscle fatigue. HFNO reduces dead space, thus increasing alveolar ventilation without altering minute ventilation ratio.²⁴ The clinical effect is a lower respiratory rate and constant tidal volume. Therefore, these patients would have less dyspnoea, perhaps providing the reason for the increased intubation rates in the conventional group. However, CO₂ clearance is thought to be dependent on flow rates.²⁵

The conventional oxygen group had significantly more patients requiring reintubation from laryngeal oedema and failed secretion clearance. The trialists suggest conditioned oxygen delivery has potential anti-inflammatory effects enabling improved clearance of secretions. However, immediate stridor after extubation is common,⁶ and it seems unlikely HFNO would have sufficient time to achieve a reduction in inflammation. Positive pharyngeal pressure may counteract nasopharyngeal collapse during inspiration through mechanical splinting of the airway and reduce stridor.²⁶ In terms of secretion management, HFNO delivers warmed, humidified gas to the nasopharynx. Conditioned gas improves mucociliary function, facilitates clearance of secretions, and is associated with less atelectasis.²⁷ The conventional oxygen therapy group did not have humidified oxygen, so perhaps humidification had a large part to play in the differences in the post-extubation failure and reintubation rates.

Where this sits in the body of evidence

FLORALI was a French multi-centre study in 310 patients with acute hypoxemic respiratory failure without hypercapnia, and a PaO₂/FiO₂ < 300 mm Hg, comparing HFNO, conventional oxygen therapy, and non-invasive positive-pressure ventilation. The intubation rate (primary outcome) was 38% in the HFNO group, 47% in the conventional group, and 50% in the non-invasive group (P=0.18). The mean (±SD) number of ventilator-free days at day 28 was significantly higher in the HFNO group (24±8 days) versus conventional oxygen group (22±10 days) and non-invasive ventilation group (19±12 days) (P=0.02). The hazard ratio for death at 90 days was 2.01 (95% CI, 1.01 to 3.99; P=0.046) with standard oxygen versus high-flow oxygen and 2.50 (95% CI, 1.31 to 4.78; P=0.006) with non-invasive ventilation versus HFNO.²¹

In a randomised, controlled, trial, 105 patients with a PaO₂/FiO₂ < 300 mm Hg before extubation were randomised to Venturi mask (n = 52) or HFNO (n = 53) for 48 hours post-extubation. After 24 hours, the mean (±SD) PaO₂/FiO₂ was higher in the high-flow group (287 ± 74 vs 247 ± 81; P=0.03). Discomfort, related both to the interface and to airway dryness, was improved with HFNO as measured on a 10 point Likert scale. Fewer patients in the HFNO group had interface displacements (32% vs 56%; P=0.01), oxygen desaturations (40% vs 75%; P<0.001), required reintubation (4% vs 21%; P=0.01), or any



form of ventilator support (7% vs 35%; $P < 0.001$).¹⁴

220 patients with intermediate to high risk of pulmonary complications after abdominal surgery were randomised to receive HFNO ($n=108$) or conventional oxygen therapy ($n=112$). The median (IQR) duration of the intervention was 16 hours (14 to 18) with standard oxygen therapy and 15 hours (12 to 18) with HFNC therapy. 21% of the HFNC patients were hypoxic one hour after extubation and 27% were hypoxic at treatment discontinuation, compared with 24% and 30% of the standard oxygen patients, respectively (adjusted RR, 4; 95% CI, -8 to 15%; $P=0.57$; adjusted RR, 0.87; 95% CI, 0.53 to 1.43; $P=0.58$). Over the 7-day follow-up period, there was no significant difference between groups in the proportion of patients without pulmonary complications (adjusted RR 7, 95% CI, -6 to 20%; $P=0.40$).²⁸

In a randomised controlled trial, 340 post cardiac surgery patients were randomised to either high-flow nasal oxygen (45 litre/min) or usual care for 48 hours. The number of patients with a SpO_2 / FiO_2 ratio of ≥ 445 on Day 3 was 78 (46.4%) in the NHF group vs 72 (42.4%) standard care OR, 1.18, 95% CI, 0.77 to 1.81, $P=0.45$]. High-flow had no effect on measures of oxygenation during or after the intervention. Infact the SpO_2 / FiO_2 ratios were actually higher in the usual care during the first 48 hours after. There was no difference in pulmonary function during the trial. However escalation in respiratory support occurred in 47 patients (27.8%) allocated to high-flow compared with 77 (45%) standard care (OR 0.47, 95% CI 0.29-0.7, $P=0.001$).²⁹

In this randomised controlled trial, 105 patients with a BMI >30 kg/m² received HFNO ($n=81$) or standard oxygen therapy ($n=74$) post cardiac surgery. No difference was seen between groups in atelectasis scores on days 1 or 5 (median scores = 2; $P=0.70$ and $P=0.15$, respectively). In the 24 hours post-extubation, there was no difference in mean PaO_2 / FiO_2 ratio (HFNO 227.9 mm Hg vs control 253.3 mm Hg, $P=0.08$), or respiratory rate.³⁰

Should we preferentially extubate low risk patients onto HFNO rather than conventional facemask oxygen?

Potentially. With no evidence of harm, and a robust signal of benefit, HFNO should be routinely considered for all patients being extubated in the ICU. Further work replicating this finding is awaited.



References

1. El-Khatib MF, Bou-Khalil P. Clinical review: Liberation from mechanical ventilation. *Critical Care*. 2008;12(4):221.
2. Kulkarni AP and Vandana A. Extubation failure in intensive care unit: Predictors and management. *Indian J Crit Care Med*. 2008; 12(1): 1–9.
3. MacIntyre NR, Cook DJ, Ely EW, Jr, Epstein SK, Fink JB, Heffner JE, Hess D, Hubmayer RD, Scheinborn DJ. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College for Critical Care Medicine. *Chest*. 2001;120:375S–395S.
4. Esteban A, Alía I, Tobin MJ, Gil A, Gordo F, Vallverdú I, et al.; Spanish Lung Failure Collaborative Group. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. *Am J Respir Crit Care Med* 1999;159:512–518.
5. Vallverdú I, Calaf N, Subirana M, Net A, Benito S, Mancebo J. Clinical characteristics, respiratory functional parameters, and outcome of a two-hour T-piece trial in patients weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1998;158:1855–1862.
6. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest* 1997;112:186–192.
7. Thille AW, Harrois A, Schortgen F, Brun-Buisson C, Brochard L. Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med* 2011;39:2612–2618.
8. Frutos-Vivar F, Ferguson ND, Esteban A, Epstein SK, Arabi Y, Apezteguía C, González M, Hill NS, Nava S, D’Empaire G, et al. Risk factors for extubation failure in patients following a successful spontaneous breathing trial. *Chest* 2006;130:1664–1671.
9. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest* 1997;112: 186-92
10. Burns KEA, Meade MO, Premji A, Adhikari NKJ. non-invasive ventilation as a weaning strategy for mechanical ventilation in adults with respiratory failure: a Cochrane systematic review. *CMAJ*. 2014; 186(3):E112-E122.
11. Itagaki T, Okuda N, Tsunano Y, Kohata H, Nakataki E, Onodera M, et al. Effect of high-flow nasal cannula on thoraco-abdominal synchrony in adult critically ill patients. *Respir Care*. 2014;59:70–4.
12. Ritchie JE, Williams AB, Gerard C, Hockey H. Evaluation of a humidified nasal high-flow oxygen system, using oxygraphy, capnography and measurement of upper



- airway pressures. *Anaesth Intensive Care*. 2011;39:1103–10.
13. Parke R, McGunness S, Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. *Br J Anaesth*. 2009;103:886–90.
 14. Maggiore SM, Idone FA, Vaschetto R, Festa R, Cataldo A, Antonicelli F et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. *Am J Respir Crit Care Med*. 2014;190(3):282-8.
 15. Ishaaya AM, Nathan SD, Belman MJ. Work of breathing after extubation. *Chest* 1995;107:204 209.
 16. Roca O, Riera J, Torres F, Masclans JR. High-flow oxygen therapy in acute respiratory failure. *Respir Care* 2010;55:408-13.
 17. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, et al. Weaning from mechanical ventilation. *Eur Respir J*. 2007;29 (5):1033-1056.
 18. Namen AM, Ely EW, Tatter SB, Case LD, Lucia MA, Smith A, et al. Predictors of successful extubation in neurosurgical patients. *Am J Respir Crit Care Med* 2001; 163:658–664.
 19. Salam A, Tilluckdharry L, Amoateng-Adjepong Y, Manthous CA. Neurologic status, cough, secretions and extubation outcomes. *Intensive Care Med*. 2004;30:1334–9.
 20. Coplin WM, Pierson DJ, Cooley KD, Newell DW, Rubenfeld GD. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. *Am J Respir Crit Care Med* 2000;161:1530–1536.20.
 21. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbetet S al; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372(23): 2185-2196.
 22. Corley A, Caruana LR, Barnett AG, Tronstad O, Fraser JF. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. *Br J Anaesth*. 2011;107(6):998–1004.
 23. Wettstein RB, Shelledy DC, Peters JI. Delivered oxygen concentrations using low-flow and high-flow nasal cannulas. *Respir Care*. 2005;50(5):604–9.
 24. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. *Respir Med* 2009;103:1400-5.
 25. Frizzola M, Miller TL, Rodriguez ME, Zhu Y, Rojas J, Heseck A, et al. High-flow nasal cannula: impact on oxygenation and ventilation in an acute lung model. *Pediatr Pulmonol*. 2011;46:67–74.
 26. Miller MJ, DiFiore JM, Strohl KP, Martin RJ. Effects of nasal CPAP on supraglottic and total pulmonary resistance in preterm infants. *J Appl Physiol* 1990;68:141-6.



27. Salah B, Dinh Xuan AT, Fouilladieu JL, Lockhart A, Regnard J. Nasal mucociliary transport in healthy subjects is slower when breathing dry air. *Eur Respir J*. 1988;1(9):852–5.
28. Futier E, Paugam-Burtz C, Godet T, Khoy-Ear L, Rozenchwajg S, Delay JM; OPERA study investigators. Effect of early post-extubation high-flow nasal cannula vs conventional oxygen therapy on hypoxaemia in patients after major abdominal surgery: a French multi-centre randomised controlled trial (OPERA). *Intensive Care Med*. 2016; 42(12):1888-1898.
29. Parke R, McGuinness S, Dixon R, Jull A. Open-label, phase II study of routine high-flow nasal oxygen therapy in cardiac surgical patients. *Br J Anaesth*. 2013;111:925–31.
30. Corley A, Bull T, Spooner AJ, Barnett AG, Fraser JF. Direct extubation onto high-flow nasal cannulae post-cardiac surgery versus standard treatment in patients with a BMI ≥ 30 : a randomised controlled trial. *Intensive Care Med*. 2015;41(5):887-94.

High-Flow Nasal Oxygen vs NIV post-extubation

Hernández G, Vaquero C, Colinas L, Cuenca R, González P, Canabal A, et al. Effect of post-extubation High-Flow Nasal Cannula vs non-invasive Ventilation on Reintubation and post-extubation Respiratory Failure in High-Risk Patients A randomised Clinical Trial. JAMA 2016;316(15):1565-1574

Introduction

Extubation failure is defined as an inability to sustain spontaneous breathing after removal of the artificial airway, with subsequent need for reintubation within a specified time period (usually up to 72 hours).¹ Failure of successful liberation from mechanical ventilation is common, with approximately 10 to 20% of patients requiring reintubation,²⁻⁶ although certain patient populations maybe at higher risk.⁵ Subsequent reintubation is associated with prolonged ventilation, increased morbidity and mortality rates of up to 50%.⁷ Consequently strategies to support ventilation after extubation to prevent the need for reintubation are appealing.

Non-invasive ventilation (NIV) has been successfully used for the treatment of respiratory failure, pulmonary oedema and in weaning from mechanical ventilation in chronic obstructive pulmonary disease.⁸ The evidence for NIV after extubation in critically ill patients is less clear. Some studies using prophylactic NIV have shown promise, although the benefits were mainly observed in patients with chronic lung disease,⁹⁻¹¹ while others have failed to replicate these results, particularly in patients without chronic lung disease.^{12,13} However, despite this, NIV use post-extubation is increasing.¹⁴ An alternative method of respiratory support is high-flow nasal oxygen (HFNO). HFNO reduces anatomical dead space,¹⁵ provides stable inspired oxygen concentrations¹⁶ and may increase lung volumes by generating low levels of end expiratory pressure.¹⁷ In a recent study of acute hypoxic respiratory failure, HFNO compared favourably with NIV.¹⁸ HFNO has also shown benefit post-extubation in patients at low risk for reintubation.^{19,20} Furthermore, when compared directly with NIV after cardiac surgery, there was no difference in outcome.²¹

Study synopsis

This open-label, non-inferiority, multi-centre, randomised trial was performed in three Spanish ICUs, and compared HFNO with NIV for the prevention of reintubation and respiratory failure after extubation. Adult patients admitted to intensive care and who were ventilated for greater than twelve hours, tolerated a spontaneous breathing trial and were considered high risk for reintubation, were eligible for recruitment. Patients were defined as high risk if they fulfilled any of the following criteria: they were greater than 65 years old, had an APACHE II score greater than 12 on the day of extubation, had a body mass index greater than 30 kg/m², were ventilated due to heart failure, suffered from moderate-to-severe COPD, had more than two predefined co-morbidities, were



unable to adequately manage respiratory secretions, were at risk of laryngeal oedema, had previously failed a trial of extubation or had prolonged mechanical ventilation (greater than 7 days). Patients were excluded if they had a do-not-resuscitate order, had a tracheostomy in-situ or had an unplanned extubation. Patients who were hypercapnic during the spontaneous breathing trial were also excluded.

Randomisation occurred after a successful spontaneous breathing trial and was performed by concealed allocation with a random-number generator through a telephone call center. Patients were randomised to HFNO or NIV. High-flow was commenced immediately following extubation with an initial flow of 10 L/min, which was increased until the patient reported discomfort. Temperature was set at 37 °C and the FiO₂ was titrated to maintain saturations above 92%. After 24 hours conventional oxygen delivery was instituted. In the NIV group, therapy was again delivered immediately via facemask with positive end-expiratory pressure (PEEP) and inspiratory pressure support adjusted to target a respiratory rate of 25/min and adequate gas exchange. The FIO₂ was adjusted to maintain SpO₂ at less than 92%. Conventional oxygen therapy was initiated after 24 hours. Sedatives were not permitted.

The primary outcomes were reintubation within 72 hours after extubation and post-extubation respiratory failure. Predefined immediate reintubation criteria for respiratory causes included: respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping respiration, psychomotor agitation despite sedation, massive aspiration, persistent unmanageable respiratory secretions, bradycardia with loss of alertness, or severe hemodynamic instability unresponsive to fluids and vasopressors. Patients were also re-intubated for persistent respiratory failure within 72 hours of extubation, defined as: a respiratory acidosis (pH <7.35 with PaCO₂ > 45 mm Hg), SpO₂ < 90% or PaO₂ less than 60 mm Hg at FiO₂ greater than 0.4, respiratory rate greater than 35/min, a decrease in Glasgow Coma Scale score >1 point, agitation, or clinical signs suggestive of respiratory muscle fatigue or increased work of breathing. The main secondary outcomes were respiratory infections, sepsis, multiorgan failure, ICU and hospital length of stay, mortality, time to reintubation, and adverse effects, including withdrawal of therapy due to patient discomfort.

Assuming a baseline reintubation rate of 20 to 25%, and with a unilateral 95% confidence interval analysis with a statistical power of 80%, 300 patients per group were required to test a 10% non-inferiority margin for the high-flow group. The non-inferiority margin was tested in both intention-to-treat and per-protocol analyses for the primary outcomes.

1,211 patients receiving mechanical ventilation for longer than 12 hours were identified with 604 (49.8%) randomised; 290 to the HFNO group and 314 to the NIV group. The majority of exclusions were due to a low risk for reintubation (77%), with hypercapnia



during a spontaneous breathing trial the next most common exclusion (10%). The groups were similar at baseline with the exception of heart failure, which was more common in the NIV group (9.9% vs 5.5%), while a surgical diagnosis at admission was more likely in the HFNO group (43.8% vs 33.4%). Randomised patients were around 64 years of age, with a mean APACHE II score of approximately 16 on admission. They had a mixture of medical and surgical conditions; primary respiratory failure (36.3%), cardiac pathology (15.0%), trauma (8.6%) and post-operative (38.4%). Prior to attempted extubation, patients had been ventilated for around four days.

At 12 hours post-extubation, the NIV group was receiving a median (IQR) FiO₂ 0.40 (35 to 50) as compared to the HFNO group, 0.35 (30 to 40), which was delivered at 50 (5) L/min. The median length of NIV was 14 hours (8 to 23). There was no difference in PaO₂ / FiO₂ (NIV 104 mm Hg vs HFNO 99 mm Hg ; P=0.83), PaO₂ (47 mm Hg vs 46 mm Hg; P=0.67) or pH (7.37 vs 7.38; P=0.57).

Overall, HFNO was noninferior to NIV, with reintubation occurring in 60 patients (19.1%) in the NIV group and 66 patients (22.8%) in the high-flow group (risk difference, -3.7%; 95% CI, -9.1% to ∞). After exclusion of non-respiratory related reintubations, the difference in reintubation rate was 50 patients (15.9%) in the NIV group vs 49 patients (16.9%) in the high-flow group (absolute difference, 1; 95% CI, -4.9 to 6.9%). However, more patients experienced respiratory failure in the NIV group (39.8% vs 26.9%; risk difference, 12.9%; 95%CI, 6.6% to ∞).

The most common reasons for reintubation were an inability to clear secretions (NIV 6.4% vs HFNO 4.5%), hypotension (3.2% vs 4.8%), and persistent respiratory failure (5.1% vs 5.5%). There was no difference in median (IQR) time to reintubation between groups {26.5 hours (14 to 39) vs 21.5 hours (10 to 47); absolute difference, -5; 95% CI, -34 to 24. The most common reasons for respiratory failure were an inability to clear secretions: (NIV 16.6% vs HFNO 10.3%), unbearable dyspnoea (8.3% vs 7.2%), hypoxia (6.1% vs 4.1%) and respiratory acidosis (6.7% vs 3.8%).

Similarly, there was no difference in various mortality endpoints (NIV vs HFNO); ICU mortality, 5.7% vs 6.6%, hospital mortality 17.8% vs 20.3%, or respiratory infections: 10.8% vs 7.9%. Median ICU length of stay after randomisation was lower in the high-flow group, 3 days (IQR, 2 to 7) vs 4 days (IQR, 2 to 9; P = 0.048). There were no adverse incidents in the HFNO group compared with 135 (42.9%) in the NIV group. This resulted in NIV being delivered for a median of 14 hours.

Study critique

Extubation after invasive ventilation is associated with increased work of breathing.²² Early support of spontaneous ventilation could improve outcomes by bridging the divide between invasive ventilation and unsupported breathing. HFNO and NIV are two such



step-down methods, but deliver support by very different means. HFNO provides a continuous flow of gas, reducing anatomical dead space and thereby improving ventilation efficiency. Small amounts of PEEP are also generated. These effects vary with flow and respiration. NIV provides support using pressure; inspiratory pressure assists inhalation and reduces work of breathing, while constant levels of PEEP recruit alveoli, improving gas exchange and lung compliance. However, NIV is not tolerated by some patients. A head-to-head trial of HFNO and NIV in post-extubation intensive care patients is clearly justified.

This trial had many strengths, including robust methodology, design and conduct. The investigators used predefined criteria for the selection of higher risk patients. There were also clear criteria for the initiation of a weaning trial, and most importantly, a comprehensive definition of failure. This ensured extubated patients fulfilled a repeatable, standardised assessment of readiness before this occurred. The trial also had criteria for reintubation (although there was clinician discretion), ensuring patients were reintubated for the same indications. Finally, there was minimal loss to followup, just 2 in each group, which is impressive in a study with over 600 patients.

There are aspects of the trial which should be considered before changing practice from NIV to HFNO in the management of the high risk post-extubation patient. Firstly, the patient population studied. Clear criteria were used to define patients who were high risk for extubation failure. Of note, 38% of patients screened were excluded for being low risk. In a recent trial these patients still had a significant extubation failure rate of 8.5%.²⁰ However, NIV was more effective than conventional oxygen therapy in similarly selected patients; therefore, considering the non inferior trial design, selection of this group of patients may increase the effectiveness of the comparator treatment. This hopefully reduces the risk of comparing two ineffective treatments. All patients had to fulfil criteria for consideration of a spontaneous breathing trial, meaning that despite being high risk for extubation failure, these patients were by definition physiologically stable. Subsequently, and different from many trials investigating NIV in weaning, these patients had to pass a spontaneous breathing trial. The breathing trial was conducted with either a T-tube or 7cmH₂O pressure support. However, very recent guidelines published by the American College of Chest Physicians and American Thoracic Society on the liberation from mechanical ventilation, suggest only pressure support breathing trials should be used, as it is associated with higher success, less reintubations and perhaps even lower mortality.²⁴

The same guidelines²⁴ recommend the use of NIV after extubation for high risk patients, defined as older, with COPD or heart failure, and hypercapnia during a spontaneous breathing trial (excluded in this trial). The guidelines do not recommend a length of treatment post-extubation. This trial intervention lasted for 24 hours, in order to prevent delayed reintubation which has been associated with increased mortality.²⁵ This

duration of treatment was similar to previous NIV trials,^{10,11} while others continued treatment until the patient either required reintubation or respiratory support could be withdrawn.^{9,21} The optimal duration of treatment to prevent reintubation is currently unclear. However, although there were differences in the patient populations, these trials delivered more NIV (in terms of hours) than the current trial and all had lower reintubation rates. Furthermore, in the two trials that recruited high risk patients,^{9,10} the trial that continued NIV after 24 hours had lower reintubation rates, suggesting dose is important.⁹ In this trial, NIV was delivered for a median of just 14 hours, in comparison to the 24 hours of HFNO. The short period of NIV is probably due to patient intolerance (and a protocol which did not allow sedation), raises questions as to the adequacy of delivery of NIV in this trial. Rather than a trial of HFNO versus NIV, it could be argued to have been a comparison of some NIV versus HFNO. There were other issues with NIV. The protocol stated two different methodologies in terms of commencing pressure support and levels of PEEP. There is no information on how the NIV gas delivery was humidified. A previous study suggested conditioned oxygen is beneficial in the post-extubation period.²⁰ In terms of trial design, these issues with the comparator make it more difficult to draw a conclusion that HFNO can be used interchangeably in this high risk population.

Despite these reservations the trial produced interesting results. There was no overall difference in the rate of reintubation, particularly when non respiratory reintubations were excluded. Causes for reintubation were similar in both groups, although consistent with the Hernandez trial incorporating HFNO in a low risk population,²⁰ the inability to clear secretion was less common in the HFNO group. Problems with management of secretions were also less common with HFNO in the respiratory failure group in this trial. Enhanced secretion management with HFNO had already been suggested as a potential benefit.¹⁹ Whether this reflects a benefit of conditioned oxygen delivery, patient comfort and better tolerance of physiotherapy, or is simply a reflection of inadequate humidification in the comparator groups is unclear. The HFNO group also had significantly less episodes of post-extubation respiratory failure. This was predominantly due to the reduction in secretion retention, but perhaps surprisingly, the NIV group suffered more hypoxia and respiratory acidosis. Despite HFNO having the capacity to improve oxygenation and lower carbon dioxide levels,¹⁹ in two previous studies the effects on oxygenation were generally inferior to NIV.^{21,26} The increased respiratory failure diagnosis in the NIV group may have subsequently been reflected in the increased length of stay in the ICU. However, this did not affect either intensive care or hospital mortality.

Where this sits in the body of evidence

In a multi-center randomised control trial, 406 patients who were ventilated for more than 48 hours and who passed a spontaneous breathing trial were randomised to either NIV (n=202) or standard medical therapy (n=204). The two groups had similar baseline



characteristics. There were no differences in extubation failure (control, 13.2% vs NIV, 14.9%), intensive care unit or hospital mortality. Overall, abundant secretions were the most common reason (35.1%) for extubation failure.¹³

The OPERA trial randomised 220 patients at intermediate-to-high risk of pulmonary complications after abdominal surgery to receive HFNO (n=108) or conventional oxygen therapy (n=112). The median duration of standard oxygen therapy was 16 hours (IQR 14 to 18) while HFNO was administered for a median of 15 hours (IQR 12 to 18). 21% of the HFNO group were hypoxic 1 hour after extubation and 27 % were hypoxic at treatment discontinuation, compared with 24% and 30% of the standard oxygen patients (ARR 4, 95 % CI -8 to 15 %; P=0.57; adjusted RR, 0.87; 95 % CI, 0.53 to 1.43; P=0.58). Over the 7-day follow-up period, there was no significant difference between the groups in the proportion of patients without any pulmonary complication (aRR, 7; 95 % CI, -6 to 20%; P=0.40).²⁷

FLORALI was a French multi-centre study in 310 patients with acute hypoxaemic respiratory failure, but without hypercapnia, who had been randomised to HFNO, standard oxygen therapy, or NIV. The intubation rate (primary outcome) was 38% in the HFNO group, 47% in the standard group, and 50% in the NIV group (P=0.18). The number of ventilator-free days at day 28 was significantly higher in the HFNO group (24±8 days, vs 22±10 in the standard-oxygen group and 19±12 in the NIV group; P=0.02). The hazard ratio for death at 90 days was 2.01 (95% CI, 1.01 to 3.99) with standard oxygen versus HFNO (P=0.046) and 2.50 (95% CI, 1.31 to 4.78) with NIV versus HFNO (P=0.006).¹⁸

In a randomised, controlled trial, 105 patients with a PaO₂/FiO₂ < 300 mm Hg before extubation were randomised to Venturi mask (n=52) or HFNO (n=53) for 48 hours. After 24 hours the PaO₂/FiO₂ was higher in the HFNO group (287 mm Hg ± 74 vs 247 mm Hg ± 81; P=0.03). Discomfort related both to the interface and to airway dryness was better tolerated with HFNO as measured on a 10 point Likert scale (respectively, 2.6 ± 2.2 vs 5.1 ± 3.3 at 24 hours; P=0.006; 2.2 ± 1.8 vs 3.7 ± 2.4 at 24 hours; P=0.002). Fewer patients had interface displacements (32% vs 56%; P=0.01), oxygen desaturations (40% vs 75%; P<0.001), required reintubation (4% vs 21%; P=0.01), or any form of ventilator support (7% vs 35%; P<0.001) in the HFNO group.¹⁹

In a multi-centre trial, 527 patients ready for extubation and considered low risk for reintubation were randomised to HFNO (n=264) or conventional oxygen therapy (n=263). Reintubation within 72 hours was less common in the HFNO group (4.9% vs 12.2%; absolute difference, 7.2%; 95% CI, 2.5% to 12.2%; P=0.004). post-extubation respiratory failure was also less common in the HFNO group (8.3% vs 14.4%; absolute difference, 6.1%; [95% CI, 0.7% to 11.6%; P=0.03). There were no adverse events.²⁰



BiPOP was a multi-center, randomised, noninferiority trial in 830 cardiothoracic surgery patients deemed at risk for respiratory failure after extubation. Patients were randomly assigned to HFNO or bilevel positive airway pressure (BiPAP). HFNO was not inferior to BiPAP; the treatment failed in 87 of 414 patients with HFNO therapy (21.0%) and 91 of 416 patients with BiPAP (21.9%) (absolute difference, 0.9%; 95% CI, -4.9% to 6.6%; P=0.003). No significant differences were found in ICU mortality (BiPAP 5.5% vs HFNO 6.8%; P=0.66; absolute difference, 1.2%; 95% CI, -2.3% to 4.8%). Skin breakdown was significantly more common with BiPAP after 24 hours.²¹

Should we implement this into our practice?

Maybe, a growing body of evidence suggests high flow nasal oxygen is helpful in the prevention of respiratory dysfunction and failure post-extubation in both low and high risk populations.

References

1. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, et al. Weaning from mechanical ventilation. *Eur Respir J*. 2007;29 (5):1033-1056.
2. Esteban A, Alía I, Tobin MJ, Gil A, Gordo F, Vallverdú I, et al.; Spanish Lung Failure Collaborative Group. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. *Am J Respir Crit Care Med* 1999;159:512–518.
3. Vallverdú I, Calaf N, Subirana M, Net A, Benito S, Mancebo J. Clinical characteristics, respiratory functional parameters, and outcome of a two-hour T-piece trial in patients weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1998;158:1855–1862.
4. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest* 1997;112:186–192.
5. Thille AW, Harrois A, Schortgen F, Brun-Buisson C, Brochard L. Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med* 2011;39:2612–2618.
6. Frutos-Vivar F, Ferguson ND, Esteban A, Epstein SK, Arabi Y, Apezteguía C, González M, Hill NS, Nava S, D’Empaire G, et al. Risk factors for extubation failure in patients following a successful spontaneous breathing trial. *Chest* 2006;130:1664–1671.
7. Thille AW, Richard JM, & Brochard L. The Decision to Extubate in the Intensive Care



Unit. *Am J Respir Crit Care Med*. 2013;187(12):1294–1302.

8. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. *Lancet*. 2009; 374(9685):250-259.
9. Nava S, Gregoret C, Fanfulla F, Squadrone E, Grassi M, Carlucci A, et al. non-invasive ventilation to prevent respiratory failure after extubation in high-risk patients. *Crit Care Med* 2005;33(11):2465-70
10. Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early non-invasive ventilation averts extubation failure in patients at risk: a randomised trial. *Am J Respir Crit Care Med*. 2006;173(2):164-70.
11. Ferrer M, Sellarés J, Valencia M, Carrillo A, Gonzalez G, Badia JR, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. *Lancet*. 2009;374(9695):1082-8.
12. Girault C, Bubenheim M, Abroug F, et al; VENISE Trial Group. non-invasive ventilation and weaning in patients with chronic hypercapnic respiratory failure: a randomised multi-centre trial. *Am J Respir Crit Care Med*. 2011;184(6):672-679.
13. Su CL1, Chiang LL, Yang SH, Lin HI, Cheng KC, Huang YC, et al. Preventive use of non-invasive ventilation after extubation: a prospective, multi-centre randomised controlled trial. *Respir Care*. 2012;57(2):204-10.
14. Demoule A, Chevret S, Carlucci A, Kouatchet A, Jaber S, Meziani F et al; oVNI Study Group; REVA Network (Research Network in Mechanical Ventilation). Changing use of non-invasive ventilation in critically ill patients: trends over 15 years in francophone countries. *Intensive Care Med*. 2016;42(1):82-92.
15. Itagaki T, Okuda N, Tsunano Y, Kohata H, Nakataki E, Onodera M, et al. Effect of high-flow nasal cannula on thoraco-abdominal synchrony in adult critically ill patients. *Respir Care*. 2014;59:70–4.
16. Ritchie JE, Williams AB, Gerard C, Hockey H. Evaluation of a humidified nasal high-flow oxygen system, using oxygraphy, capnography and measurement of upper airway pressures. *Anaesth Intensive Care*. 2011;39:1103–10.
17. Parke R, McGunness S, Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. *Br J Anaesth*. 2009;103:886–90.
18. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbetet S al; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372(23): 2185-2196.
19. Maggiore SM, Idone FA, Vaschetto R, Festa R, Cataldo A, Antonicelli F et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. *Am J Respir Crit Care Med*. 2014;190(3):282-8.
20. Hernández G, Vaquero C, González P, et al. Effect of post-extubation high-flow nasal



cannula vs conventional oxygen therapy on reintubation in low-risk patients: a randomised clinical trial. *JAMA*. 2016;315(13):1354-1361.

21. Stéphan F, Barrucand B, Petit P, Rézaiguia-Delclaux S, Médard A, Delannoy B, et al. High-Flow Nasal Oxygen vs non-invasive Positive Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery: A randomised Clinical Trial. *JAMA*. 2015;313(23):2331-9.
22. Ishaaya AM, Nathan SD, Belman MJ. Work of breathing after extubation. *Chest* 1995;107:204-209.
23. Glossop AJ, Shephard N, Bryden DC, Mills GH. Non-invasive ventilation for weaning, avoiding reintubation after extubation and in the post-operative period: a meta-analysis. *Br J Anaesth*. 2012;109(3):305-314.
24. Schmidt GA, Girard TD, Kress JP, Morris PE, Ouellette DR, Alhazzani W, et al. Liberation from Mechanical Ventilation in Critically Ill Adults: Executive Summary of an Official American College of Chest Physicians / American Thoracic Society Clinical Practice Guideline. *Chest* 2017;151(1):160-165
25. Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apezteguía C, González M et al. non-invasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med*. 2004;350(24):2452-2460.
26. Schwabbauer N, Berg B, Blumenstock G, Haap M, Hetzel J, Riessen R. Nasal high-flow oxygen therapy in patients with hypoxic respiratory failure: effect on functional and subjective respiratory parameters compared to conventional oxygen therapy and non-invasive ventilation (NIV). *BMC Anesthesiol*. 2014;14:66.
27. Futier E, Paugam-Burtz C, Godet T, Khoy-Ear L, Rozenchwajg S, Delay JM; OPERA study investigators. Effect of early post-extubation high-flow nasal cannula vs conventional oxygen therapy on hypoxaemia in patients after major abdominal surgery: a French multi-centre randomised controlled trial (OPERA). *Intensive Care Med*. 2016; 42(12):1888-1898.

OPERA

Futier E, Paugam-Burtz C, Godet T, Khoy-Ear L, Rozencwajg S, Delay JM et al. Effect of early post-extubation high-flow nasal cannula vs conventional oxygen therapy on hypoxaemia in patients after major abdominal surgery: a French multi-centre randomised

Introduction

Respiratory complications occur in up to 10% of patients after abdominal surgery and are associated with adverse short and long term survival.^{1,2} General anaesthesia is associated with reductions in lung volumes, ventilation-perfusion mismatch and impairment of pulmonary defence mechanisms.³ Furthermore, it is increasingly recognised that intra-operative mechanical ventilation is associated with lung injury and that optimal ventilation is important in the reduction of respiratory complications.⁴ However, despite lung protective strategies, respiratory complications remain a common complication after surgery.⁵ non-invasive ventilation has been investigated in the prevention of post-operative complications, with a recent meta-analysis suggesting post-operative use might reduce atelectasis, pneumonia and reintubation.⁶ However, uncertainties regarding the benefits of post-operative ventilation remain. non-invasive ventilation may not be tolerated by some patients, reducing potential benefits. High flow nasal oxygen (HFNO) has been used as an alternative means of respiratory support. HFNO reduces anatomical dead space, provides stable inspired oxygen concentrations and may increase lung volumes by generating low levels of positive end expiratory pressure.⁷ In clinical trials HFNO has compared favourably with non-invasive ventilation in acute respiratory failure, post-extubation in cardiac surgery and intensive care.⁸⁻¹⁰ The OPERA trial aimed to investigate the effects of HFNO after abdominal surgery.

Study synopsis

This was a non blinded, multi-centre, randomised trial performed in three intensive care units in France. The aim was to establish the superiority of HFNO over conventional oxygen therapy after prolonged abdominal surgery for the prevention of post-operative hypoxaemia.

All adult patients scheduled for abdominal surgery, with or without thoracic access, an anticipated duration of over two hours, and with a moderate-to-high risk of post-operative complications defined by the ARISCAT risk score, were eligible for recruitment.¹¹ Patients were excluded if surgery was an emergency, they had a body mass index greater than 35 kg/m², had obstructive sleep apnoea or were pregnant. Randomisation was performed using a computer generated assignment sequence in a 1:1 ratio, with stratification by centre and planned use of an epidural for analgesia. Patients were randomised to HFNO or conventional post-operative oxygen therapy via



nasal prongs or facemask. HFNO was commenced immediately post-extubation with a gas flow rate of 50-60 L/min. In both groups oxygen therapy was titrated to maintain saturations above 95%. As per the protocol all patients were to have standardised intra-operative lung protective ventilation, which consisted of low tidal volumes, moderate PEEP and recruitment manoeuvres. The intervention period lasted until the first post-operative morning when patients were administered conventional oxygen as required to maintain saturations above 93%. All other interventions were at the discretion of the treating physicians.

The primary outcome was the development of hypoxaemia, defined as a $\text{PaO}_2/\text{FiO}_2$ less than 300 mm Hg or less measured one hour after extubation. This outcome was also measured after the intervention ended. Blood gases were performed on room air. The main secondary outcomes were respiratory events over the first post-operative week and at hospital discharge. Respiratory events were post-operative pulmonary complications due to any cause, requirement for oxygen supplementation after discontinuation of the intervention and development of post-operative hypoxaemia, pneumonia, reintubation or requirement for non-invasive ventilation. The requirement for intensive care, hospital and ICU length of stay and mortality were also recorded.

Assuming an incidence of hypoxaemia of 40% after extubation, 220 patients were required to detect a relative difference of 50% in the primary outcome, with 90% power at a two sided alpha level of 0.05. All analyses were performed on an intention-to-treat principle. An interim safety analysis was planned after half the patients were recruited.

691 patients were screened, of which 303 patients were ineligible due to a low risk of pulmonary complications on the ARISCAT score or too short an anticipated duration of surgery. Of the 388 who met initial inclusion criteria, 23 declined to participate, 45 had an exclusion criteria, and 100 patients were enrolled in another trial. 220 patients were subsequently randomised, 112 patients to the usual care and 108 patients to the HFNO group. The two groups had similar baseline characteristics. Randomised patients were around 61 years of age, with a BMI of 25 kg/m^2 . The majority of patients were ASA 2 (66.8%), 27% were smokers and the most common co-morbidity was hypertension (31%). There were minimal patients with prior respiratory disease. The majority of operations were elective (99%) procedures with a cancer diagnosis (81.3%) and were performed by midline incision in 46.8% and by a transverse incision in 42.3% of patients. Typical surgery lasted around 5 hours. In terms of the intra-operative management, again the two groups had similar treatment. Tidal volumes were approximately 7.5 ml/kg, PEEP 6 cmH_2O and two thirds of patients had at least one recruitment manoeuvre performed. Epidural rates were similar (33% usual care vs 34% HFNO). Blood loss was about 350mls in each group. Patients in the usual care group received more crystalloid (3000 ml vs 2500 ml) and more colloid (1000 ml vs 750 ml), neither were statistically significant. The intervention was commenced on all patients for a median of 16hrs (IQR 14 to 18hrs)



post-extubation. Eight patients were unable to tolerate the intervention.

Overall there was no difference in the primary outcome, 21% of patients in the HFNO and 24% of patients in the conventional care group had post-operative hypoxaemia one hour after surgery (absolute RR, 3%; 95% CI, -14 to 8%; P=0.62). At the discontinuation of the intervention 27% vs 30% of patients experienced hypoxaemia (ARR, 4 %; 95% CI, -8 to 15%, P=0.57). There were no significant between-group differences for any of the secondary outcomes: need for supplemental oxygen therapy for persistent hypoxaemia, pulmonary complications, number of patients requiring any form of ventilatory assistance during the first 7 days after surgery, and service utilization (days in ICU or in hospital). In hospital mortality rates were low (3 patients usual care versus 2 patients HFNO). In a post hoc analysis, there was a significant interaction between the use of recruitment manoeuvres and the intervention group, with respect to hypoxaemia after discontinuation of the intervention. However, the effect of HFNO on the primary outcome remained non-significant.

Study critique

Oxygen is routinely administered after mechanical ventilation in order to maintain adequate tissue oxygenation. Alveolar collapse and atelectasis occur in up to 90% of patients after surgery; this contributes to post-operative hypoxaemia and may cause major complications following extubation.⁴ Appropriate intra-operative ventilation may reduce atelectasis, however, these strategies may not result in sustained benefit.¹² Therefore, continued respiratory support post-extubation during spontaneous breathing, and before respiratory failure develops, could significantly improve patient outcomes. There has been recent focus on the role of non-invasive ventilation,⁶ however a therapy that can be delivered outside of critical care could have significantly more impact.

This is the largest study investigating the effects of HFNO after abdominal surgery. The trial has several noteworthy strengths which add to the quality of the research. The inclusion criteria sought to enrol patients who were most likely to develop post-operative respiratory complications, and therefore logically increase the chance of discovering a treatment effect. This was done using the ARISCAT risk score.¹¹ The Assess Respiratory Risk in Surgical Patients in CATalonia study was conducted in a general surgical population in Spain. It identified seven risk factors which were internally validated with an area under the receiver operating curve of 0.9 (95% CI, 0.85 to 0.94). The score was externally validated in a large European surgical sample (the Prospective Evaluation of a Risk Score for post-operative Pulmonary COMplications in Europe study)¹³ and hence probably represents the most accurate tool for the prediction of post-operative respiratory complications. The investigators excluded patients with a high body mass index, which initially seems to exclude a population with a high risk of pulmonary complications; however, a preventative study in cardiac surgery patients



(another population at high risk of post-operative respiratory complications) failed to identify a benefit of HFNO.¹⁴ This careful selection of study patients perhaps again increased the likelihood of a positive outcome. Exclusion of life threatening emergency patients, however, does limit the conclusions of the study to planned surgical procedures. A further strength of the trial was the randomisation process. This was stratified by both site and by the planned use of epidural analgesia, which may influence respiratory complications in post-operative patients;¹⁵ therefore, ensuring an even distribution of this intervention would should eliminate a confounding variable. Although epidural analgesia was used in around one third of patients in this study, this may not reflect the current peri operative use in other countries.¹⁶ The randomisation process resulted in balanced groups in terms of co-morbidities, surgery performed and predicted risk of respiratory complications. Finally, in terms of the protocol there were two interventions which add to the quality of the research. Firstly, the trialists attempted to eliminate the influence of intra-operative ventilation on post-operative lung complications by stipulating a lung protective ventilation strategy. Although not all patients had recruitment manoeuvres, the tidal volumes and PEEP used were within recommendations for intra-operative patients without lung injury and the plateau pressures were generally low.⁴ Secondly, in the intervention group, gas flow was between 50-60 L/min, which would generate low levels of PEEP and therefore again maximise the potential benefit of the therapy.

The OPERA trial failed to show a difference in outcome with prophylactic HFNO compared with standard oxygen therapy. This is despite several trials showing similar results with non-invasive ventilation,⁸⁻¹⁰ and meta-analysis concluding that non-invasive ventilation was beneficial in post-operative prophylaxis.⁶ There are some aspects of this trial to consider before abandoning HFNO prophylaxis.

The study used a surrogate outcome, hypoxaemia, as a primary outcome rather than a more patient centred outcome. The investigators justified this because hypoxaemia maybe a factor associated with poor patient outcomes. The use of surrogate outcomes may allow for a reduction in sample size, but surrogate outcomes can be more sensitive to the effect of the therapeutic interventions than patient-oriented outcomes, leading to over-estimation of intervention effects.¹⁷ The definition of hypoxaemia in this trial, PaO₂/FiO₂ less than 300 mm Hg, was previously used as a selection criteria in a prophylactic non-invasive ventilation trial¹⁸ and correlates with the hypoxia associated with mild ARDS. However, there is limited evidence this degree of post-operative lung dysfunction correlates with poor peri operative outcomes or that correction improves clinical outcomes. In addition, the measurement was performed at a single time point rather than over a period of time as in the positive non-invasive trial.¹⁸ This could share similarities with previous ARDS trials; where a single PaO₂/FiO₂ was used to recruit patients, who subsequently rapidly improved after the application of a simple intervention such as increased PEEP. Finally, in a recent post-extubation trial in critical



care, patient outcomes were improved with HFNO despite minimal effects on PaO₂/FiO₂.¹⁹ A further limitation of the trial was the assumption that the intervention would reduce the incidence of hypoxaemia by 50%. Although the trial used a physiological outcome it is still perhaps optimistic the intervention would have such a profound effect. Perhaps a larger trial with more patient-centred outcomes may have answered more pertinent questions.

The intervention delivered in this trial was HFNO at a gas flow rate of 50-60 L/min, initiated after extubation and continued until the following morning after surgery (approximately 15 hours). The predominant cause of early post-operative hypoxaemia is atelectasis,²⁰ and therefore an important mechanism for reversal in the post-operative period is positive end expiratory pressure. HFNO at 60 L/min can produce up to 7 cmH₂O of positive airway pressure measured in the upper airway. However, the level of positive airway pressure is likely to be much lower, is dependent on whether the mouth is open and varies between patients.⁷ Previous positive trials with prophylactic non-invasive ventilation in cardiac surgery, thoraco-abdominal aneurysms and after abdominal surgery have used between 7.5 cmH₂O and 10 cmH₂O.^{18,21,22} These levels of PEEP are likely to be higher than levels produced by HFNO. High levels of CPAP have been shown to reverse post-operative atelectasis.²³ Perhaps the failure of HFNO in this study, and in two cardiac surgery populations,^{14,24} at least in terms of gas exchange, relates to insufficient levels of PEEP. It is noteworthy that despite little effect on gas exchange, escalation in respiratory support was reduced in the largest cardiac surgery population.²⁴ Hence gas exchange per say may not reflect the beneficial effects with HFNO. Timing and duration of therapy may also influence outcomes. The duration of treatment was longer in several of the non-invasive ventilation trials,^{18,22} and in studies where HFNO compared favourably to non-invasive ventilation,⁸⁻¹⁰ as well as in a post-extubation critical care population.²⁵ However, HFNO was successful used for only 12 hours in a low risk critical care population.¹⁹ Collectively, although these studies recruited a diverse patient population with differing pathologies, it may be that the cause of respiratory failure determines the effectiveness of HFNO in improving respiratory status. Further research is required in terms of duration of therapy in the post-operative period.

Finally, the population studied in this trial also needs to be carefully considered. These patients were relatively young (61 years of age), two thirds of patients were ASA grade two, with relatively limited numbers of co-morbidities and only moderate ARISCAT risk scores. Perhaps this reflects the reason for the lower incidence of hypoxaemia encountered in the trial than predicted in the power calculation. The type of operations, were predominantly upper gastrointestinal procedures involving the liver or pancreas. These procedures lasted a median of between 4.5 and 5 hours. There were almost equal numbers of patients with transverse incisions compared to traditional midline wounds. Although the trial attempted to enrol a high risk population, there is a juxtaposition between the patients and the type of surgery, with seemingly the surgery the main risk.



It is hard to compare to the typical elderly patient with multiple co-morbidities having a relatively straightforward laparotomy for bowel cancer in a district general hospital.

Where this sits in the body of evidence

In a pragmatic trial, 340 patients were randomised to either HFNO (45 L/min) or usual care from extubation to day 2 after cardiac surgery. There was no difference in the number of patients with $SpO_2/FiO_2 \geq 445$ on day 3 (HFNO, 46.4% vs usual care, 42.4%; OR, 1.18; 95% CI, 0.77 to 1.81; $P=0.45$). $PaCO_2$ was reduced at both 4 hours post-extubation and on day 1 in the HFNO group (5.3 vs 5.4 kPa, $P=0.03$; and 5.1 vs 5.3 kPa, $P=0.03$; respectively). Escalation in respiratory support at any time in the study occurred in 27.8% allocated to HFNO compared with 45% receiving standard care (OR, 0.47; 95% CI, 0.29 to 0.7; $P=0.001$).²⁴

In a randomised controlled trial, 155 obese patients ($BMI >30 \text{ kg/m}^2$) post cardiac surgery were assigned to either HFNO ($n=81$) or standard oxygen therapy ($n=74$) post-extubation. The primary outcome was atelectasis on chest X-ray. There was no difference between groups in atelectasis scores on days 1 or 5 (median scores=2; $P=0.70$; and $P=0.15$, respectively). In the 24 hour post-extubation period, there was no difference in mean PaO_2/FiO_2 (HFNO, 227.9 vs control, 253.3; $p = 0.08$), or respiratory rate (HFNO 17.2, control 16.7, $p = 0.17$).¹⁴

In a randomised, controlled, unblinded study 209 patients with severe hypoxemia after major elective abdominal surgery were randomly assigned to receive oxygen ($n = 104$) or oxygen plus continuous positive airway pressure (CPAP) ($n = 105$). Patients who received CPAP had a lower intubation rate (1% vs 10%; $P=0.005$; RR, 0.099; 95% CI, 0.01 to 0.76) and had a reduced incidence of pneumonia (2% vs 10%; RR, 0.19; 95% CI, 0.04 to 0.88; $P=0.02$), infection (3% vs 10%; RR, 0.27; 95% CI, 0.07 to 0.94; $P=0.03$), and sepsis (2% vs 9%; RR, 0.22; 95% CI, 0.04 to 0.99; $P=0.03$). CPAP patients who also spent fewer mean (SD) days in the intensive care unit, 1.4 (1.6) vs 2.6 (4.2); $P=0.09$). There was no difference in length of hospital stay or mortality.¹⁸

In a randomised single-centre trial, 50 patients post-elective replacement of the thoracoabdominal aorta were extubated to either continuous CPAP for 12 to 24 hours at an airway pressure of 10 cmH_2O or to standard treatment, including intermittent CPAP (10 $\text{cm H}_2\text{O}$ for 10 min) every 4 hrs. In the intervention group, CPAP was applied for a mean (\pm SD) duration of 23 ± 3 hours. CPAP was associated with fewer pulmonary complications ($PaO_2/FiO_2 < 100$, atelectasis, pneumonia, reintubation rate) compared to the control group (7 of 25 patients vs 24 of 25 subjects, respectively; $P=0.019$). While there was no difference in ICU length of stay, the mean hospital length of stay was shorter with CPAP therapy (22 ± 2 vs 34 ± 5 days, respectively; $P=0.048$).²¹

In a single-centre randomised trial 500 patients post-elective cardiac surgery were



allocated to standard treatment, including 10 minutes of intermittent nasal CPAP at 10 cm H₂O every 4 h, or prophylactic nasal CPAP at an airway pressure of 10 cm H₂O for at least 6 hours. Prophylactic CPAP significantly improved arterial oxygenation (PaO₂/FiO₂) without altering heart rate and mean arterial BP. Pulmonary complications, including hypoxemia (defined as PaO₂/FiO₂ <100 mm Hg), pneumonia, and reintubation rate were reduced in the intervention group compared to controls (12 of 232 patients vs 25 of 236 patients, respectively; P=0.03). The readmission rate to the ICU was significantly lower in CPAP-treated patients (7 of 232 patients vs 14 of 236 patients, respectively; P=0.03).²¹

In the multi-center, randomised, noninferiority BiPOP trial, 830 cardiothoracic surgery patients deemed high risk for respiratory failure after extubation were randomly assigned to HFNO or bilevel positive airway pressure. HFNO was not inferior to BiPAP. The treatment failed in 21.0% of the HFNO group and 21.9% of the BiPAP group; absolute difference, 0.9%; 95% CI, -4.9% to 6.6%; P=0.003). There was no significant difference in ICU mortality (BiPAP, 5.5% vs HFNO, 6.8%; P=0.66) (absolute difference, 1.2%; 95% CI, -2.3% to 4.8%. Skin breakdown was significantly more common with BiPAP after 24 hours.⁹

Should we routinely use HFNO after major abdominal surgery?

Possibly. Although the OPERA trial did not demonstrate improvements with HFNO after major abdominal surgery, a number of large robust randomised controlled trials in other settings suggest benefit with this intervention.

References

1. Lawrence VA, Hilsenbeck SG, Mulrow CD, Dhanda R, Sapp J, Page CP. Incidence and hospital stay for cardiac and pulmonary complications after abdominal surgery. *J Gen Intern Med.* 1995; 10(12):671-8.
2. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of post-operative complications. *Annals of surgery* 2005; 242(3): 326-43.
3. Richardson J & Sabanathan S. Prevention of respiratory complications after abdominal surgery. *Thorax* 1997; 52(Suppl 3):S35–S40.



4. Güldner A, Kiss T, Neto AS, Hemmes S, Canet J, Spieth PM, et al. intra-operative Protective Mechanical Ventilation for Prevention of post-operative Pulmonary Complications. *Anesthesiology* 2015; 123:692–713.
5. Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multi-centre randomised controlled trial. *Lancet* 2014; 384:495–503.
6. Ireland CJ, Chapman TM, Mathew SF, Herbison GP, Zacharias M. Continuous positive airway pressure (CPAP) during the post-operative period for prevention of post-operative morbidity and mortality following major abdominal surgery. *The Cochrane database of systematic reviews* 2014; 8: CD008930.
7. Ricard JD. High flow nasal oxygen in acute respiratory failure. *Minerva Anestesiol* 2012; 78:836-41.
8. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbetet S al; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med.* 2015; 372(23): 2185-2196.
9. Stéphan F, Barrucand B, Petit P, Rézaiguia-Delclaux S, Médard A, Delannoy B, et al. High-Flow Nasal Oxygen vs non-invasive Positive Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery: A randomised Clinical Trial. *JAMA.* 2015; 313(23):2331-9.
10. Hernández G, Vaquero C, Colinas L, Cuenca R, González P, Canabal A, et al. Effect of post-extubation High-Flow Nasal Cannula vs non-invasive Ventilation on Reintubation and post-extubation Respiratory Failure in High-Risk Patients A randomised Clinical Trial. *JAMA.* 2016; 316(15):1565-1574.
11. Canet J, Gallart L, Gomar C, Paluzie G, Valles J, Castillo J, et al. Prediction of post-operative pulmonary complications in a population-based surgical cohort. *Anesthesiology* 2010; 113:1338–1350.
12. Lumb AB, Greenhill SJ, Simpson MP, Stewart J. Lung recruitment and positive airway pressure before extubation does not improve oxygenation in the post-anaesthesia care unit: a randomised clinical trial. *BJA* 2010; 104:643–647.
13. Mazo V, Sabaté S, Canet J, Gallart L, Gama de Abreu M, Belda J, et al. Prospective external validation of a predictive score for post-operative pulmonary complications. *Anesthesiology* 2014; 121:219–31.
14. Corley A, Bull T, Spooner AJ, Barnett AG, Fraser JF (2015) Direct extubation onto high-flow nasal cannulae post-cardiac surgery versus standard treatment in patients with a BMI ≥ 30 : a randomised controlled trial. *Intensive Care Med* 2015; 41:887–894.
15. Popping DM, Elia N, Marret E, Remy C, Tramer MR. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a



meta-analysis. *Arch Surg* 2008; 143:990–999.

16. Christie I, McCabe S. Major complications of epidural analgesia after surgery: results of a six-year survey. *Anaesthesia* 2007; 62:335–341.
17. Ciani O, Buyse M, Garside R, Pavey T, Stein K, Sterne J, et al. Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomised controlled trials: meta-epidemiological study. *BMJ* 2013; 346: f457.
18. Squadrone V, Coia M, Cerutti E, Schellino MM, Biolino P, Occella P et al. Continuous positive airway pressure for treatment of post-operative hypoxemia: a randomised controlled trial. *J Am Med Assoc* 2005; 293: 589–95.
19. Hernández G, Vaquero C, González P, Subira C, Frutos-Vivar F, Rialpet G al. Effect of post-extubation High-FlowNasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients- A randomised Clinical Trial *JAMA* 2016; 315(13):1354-61.
20. Jaber S, Lescot T,MD, Futier E, Paugam-Burtz C, Seguin, Ferrandiere M et al. Effect of non-invasive Ventilation on Tracheal Reintubation Among Patients With Hypoxemic Respiratory Failure Following Abdominal Surgery A randomised Clinical Trial. *JAMA* 2016; 315(13):1345-53.
21. Zarbock A, Mueller E, Netzer S, Gabriel A, Feindt P &Kindgen-Milles D. Prophylactic nasal continuous positive airway pressure following cardiac surgery protects from post-operative pulmonary complications: a prospective, randomised, controlled trial in 500 patients. *Chest* 2009; 135: 1252–9.
22. Kindgen-Milles D, Muller E, Buhl R, Böhner H, Ritter D, Sandmann W et al. Nasal-continuous positive airway pressure reduces pulmonary morbidity and length of hospital stay following thoracoabdominal aortic surgery. *Chest* 2005; 128: 821–8.
23. Lindner KH, Lotz P, Ahnefeld FW. Continuous positive airway pressure effect on functional residual capacity, vital capacity and its subdivisions. *Chest* 1987; 92(1):66-70.
24. Parke R, McGuinness S, Dixon R, Jull A (2013) Open-label, phase II study of routine high-flow nasal oxygen therapy in cardiac surgical patients. *BJA* 2013; 111:925–931.
25. Maggiore SM, Idone FA, Vaschetto R, Festa R, Cataldo A, Antonicelli F et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. *Am J Respir Crit Care Med*. 2014; 190(3):282-8.

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Jaber S, Lescot T,MD, Futier E, Paugam-Burtz C, Seguin, Ferrandiere M et al. Effect of non-invasive Ventilation on Tracheal Reintubation Among Patients With Hypoxemic Respiratory Failure Following Abdominal Surgery A randomised Clinical Trial. JAMA 2016;3

Introduction

Of 312 million operations performed every year, approximately 10 to 20% of patients suffer complications and up to 4% die.^{1,2} Acute respiratory failure is amongst the most common post-operative complications and can adversely affect both short and long term survival.³ A recent study has shown higher mortality rates associated with intra abdominal procedures.⁴ Major abdominal surgery is associated with a reduction in respiratory function. Anaesthesia and surgery causes a reduction in functional residual and vital capacities, abnormalities of gas exchange, altered ventilation and impairment of mucociliary clearance predisposing to pulmonary complications.⁵ Whilst preventive measures may reduce respiratory complication rates⁶, the most beneficial treatment after the onset of acute post-operative respiratory failure is unknown. Intubation and mechanical ventilation can be life saving but is associated with complications.⁷ non-invasive ventilation has been successfully used for the treatment of respiratory failure, pulmonary oedema and in weaning from mechanical ventilation in chronic obstructive pulmonary disease.⁸ However, when used as rescue therapy after extubation in critical care patients non-invasive ventilation may even be associated with harm.⁹ Although undoubtedly used for post-operative acute respiratory failure, there is limited evidence of the efficacy to support its use.

Study synopsis

This was an open-label multi-centre, randomised trial performed in twenty intensive care units in France. The aim of the study was to establish if non-invasive ventilation improved outcome in hypoxic respiratory failure after abdominal surgery.

All post-operative patients who had either laparoscopic or open abdominal surgery were screened. Patients were included if they developed acute respiratory failure within seven days of surgery, defined as: a minimum of 30 minutes of hypoxaemia (arterial oxygen partial pressure <60 mm Hg or saturation <90% breathing room air or <80 mm Hg on 15 L/min oxygen), plus either a respiratory rate >30/min or clinical signs of increased work of breathing or respiratory distress (such as intercostal retraction or paradoxical abdominal wall movement). Patients were excluded if they required immediate intubation, had a contra-indication to non-invasive ventilation, obstructive sleep apnoea or a limitation of treatment.



Patients were randomised using a computer-generated and blinded assignment sequence. randomisation was stratified according to study site, age (less than or greater than 60 years), site of surgery (upper or lower abdominal) and according to the use of post-operative epidural analgesia. Patients were assigned to either standard oxygen therapy at a rate of up to 15 L/min to maintain SpO₂ above 94% or to non-invasive ventilation via facemask for the duration of intensive care stay. non-invasive ventilation was commenced with an inspiratory pressure of 5 cmH₂O and a PEEP of 5 cmH₂O. The inspiratory pressure was increased up to 15 cmH₂O to maintain tidal volumes between 6 and 8 ml/kg predicted body weight and a respiratory rate of less than 25/min. PEEP and inspired oxygen fraction were adjusted in the standard oxygen group to maintain SpO₂ above 94%. Maximum PEEP was set at 10 cmH₂O. The investigators aimed for a minimum of six hours of non-invasive ventilation in the first 24 hours, with conventional oxygen administered when non-invasive ventilation was not used. Discontinuation of non-invasive ventilation was at the discretion of the treating physicians.

The primary outcome was reintubation within 7 days after randomisation. Predefined immediate reintubation criteria for respiratory causes included respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping respiration, psychomotor agitation despite sedation, massive aspiration, persistent unmanageable respiratory secretions, bradycardia with loss of alertness, or severe hemodynamic instability unresponsive to fluids and vasopressors. Predefined causes and timing of reintubation were also recorded. Secondary outcomes included arterial blood gas comparison, hospital-acquired infections, antibiotic use, ventilator-free days, ICU and hospital lengths of stay, and 30 and 90 day mortality.

Assuming a 65% rate of reintubation in the conventional oxygen group, 150 patients per group were required to identify a 25% absolute reduction in the non-invasive ventilation group, with 90% power at the 5% significance level, and allowing for 15% loss to follow up. Two planned interim safety analysis were performed after 100 and 200 patients. A priori subgroups were as per stratification.

535 patients who developed hypoxic respiratory failure were screened. 235 patients were excluded, mainly due to enrolment in another study (38%), reoperation (20%) or sleep apnoea (13%). 150 patients were randomised to each group. Five patients were subsequently excluded from the conventional therapy group and two from the non-invasive ventilation group. The baseline characteristics were similar in each group. Patients were around 63 years of age, mainly male with a body mass index about 27 kg/m². At randomisation around 50% of patients had cancer, 25% had sepsis and there were prevalent rates of smoking (29%) and alcohol abuse (18%). Surgical procedures and total operating times (approx 4 hours) were similar. 48% of operations were emergency procedures, with the majority of operations performed by open laparotomy (91%). Only 46 patients received epidural analgesia. Post operation, 37% of patients were still



ventilated after six hours.

Patients in the conventional group had a mean oxygen flow of 10.4 L/min. Patients in the non-invasive ventilation group had a mean inspiratory pressure of 6.7 cmH₂O, a mean PEEP of 5.4 cmH₂O and an FiO₂ of 0.5. The mean tidal volume was 8.3 ml/kg predicted body weight. non-invasive ventilation was administered for a mean of 7.4 hours in the first 24 hours and for a median of 4 days (IQR 1 to 5).

non-invasive ventilation reduced the reintubation rate after seven days, 33.1% vs 45.5%; absolute difference, -12.4%; 95% CI, -23.5% to -1.3%; P=0.03). There was no difference in time to reintubation (standard oxygen group, median 1 day (IQR 1 to 3 days) vs non-invasive group, 2 days (1 to 6); absolute difference with standard care 0.66, 95% CI, -0.76 to 2.09; P=0.08) or reasons for reintubation (56% were reintubated for continued respiratory distress).

Gas exchange was not significantly different between the groups. However at 30 days there were significantly more ventilator-free days in the non-invasive group (25.4 vs 23.2 days; absolute difference, -2.2 days; 95% CI, -0.1 to 4.6 days; P=0.04). However, there was no difference in intensive care length of stay or hospital length of stay. Hospital length of stay was lower in the non-invasive group when only survivors were analysed. The non-invasive group had less hospital acquired infections (31.4% vs 49.2%; absolute difference, -17.8%; 95% CI, -30.2% to -5.4%; P = 0.003) due to a reduction in episodes of pneumonia (14.6% vs 29.7%; P = 0.003). Overall, there was no difference in 30 or 90 day mortality. There were no serious adverse events reported in either group. The most severe reported issue with non-invasive ventilation was mask leak.

Study critique

This trial enrolled post-operative abdominal surgery patient who had developed acute hypoxaemic respiratory failure. Traditionally non-invasive ventilation has been used for exacerbations of chronic obstructive pulmonary disease or cardiogenic pulmonary oedema. Hypoxaemic respiratory failure represents a more diverse heterogeneous population and the evidence for non-invasive in these patients is less robust. However, the rationale for use of non-invasive ventilation to improve oxygenation and reduce respiratory muscle workload is attractive. Furthermore, the avoidance of intubation and its inherent complications may improve outcome, but this must be balanced against the potential risks of delayed intubation. Results for non-invasive ventilation in hypoxaemic patients have been mixed, although non-invasive ventilation has shown some physiological benefits, including reductions in intubation requirements and complications. However, failure rates can be high.¹⁰ A recent Cochrane review identified only two randomised trials incorporating a total of 269 patients using non-invasive ventilation for post upper abdominal surgery respiratory failure.¹¹ Although the review concluded that non-invasive ventilation was an effective treatment, the quality of the



evidence was questioned.

This trial is currently the largest study investigating the effect of non-invasive ventilation for post-abdominal surgery respiratory failure. The trial has several strengths. In terms of safety, the trial had criteria for immediate intubation. Although this would have excluded some patients, the criteria prevented trials of inappropriate non-invasive ventilation and potential harmful delays in intubation. A further safety concern in any ventilation trial is lung injury caused by large tidal volumes and high pressures. Hypoxic respiratory failure is usually associated with a high respiratory drive. Experimentally-induced high tidal volumes in spontaneously breathing animals may induce lung injury.¹² non-invasive ventilation increases alveolar ventilation by increasing the transpulmonary pressure with supported breaths, thus generating larger tidal volumes. The protocol prevented inappropriately high tidal volumes by targeting 6-8 ml/kg ideal body weight. Subsequently, when a patient met inclusion criteria, the randomisation process included stratification of several factors which may have influenced outcomes, ensuring balanced groups in the treatment and control arms of the study. After randomisation there were only a limited number of withdrawals and no patients lost to follow up. The protocol also had predefined causes for respiratory failure and recognised definitions for infectious complications.

Treatment of hypoxic respiratory failure with non-invasive ventilation is associated with significant failure rates and requirement for intubation.¹³ Failure of non-invasive ventilation has been associated with increased disease severity, haemodynamic instability, lower Glasgow Coma Scale score and more severe hypoxaemia.¹⁴ Therefore, careful selection of patients is likely to be important in the prevention of a futile intervention. It is worth noting that patients in this trial who did not require immediate intubation still had to be deemed suitable for non-invasive ventilation. Patients with hemodynamic instability, defined by systolic arterial blood pressure below 90 mm Hg or a mean arterial blood pressure below 65 mm Hg, the requirement for vasopressors, or a Glasgow Coma Scale score of 12 or less were excluded. These rigorous exclusion criteria resulted in patients with a relatively low SAPS II scores and a low overall predicted mortality. Interpretation of the results should be taken in the context of this patient selection.

A further consideration in the design of this trial was the use of non-invasive ventilation as a rescue therapy for hypoxic respiratory failure. Several previous peri operative trials and one current trial have concentrated on prophylactic non-invasive ventilation rather than as a rescue technique.¹⁵⁻¹⁸ These trials have demonstrated efficacy of prophylactic continuous positive airway pressure (CPAP) ventilation. Arguably efforts to further identify patients who would benefit from prevention rather than rescue would be more useful. However, the strength of evidence for prophylactic CPAP is limited by trial size and heterogeneity of the intervention; in addition, a cost analysis of prophylaxis has not



been performed. There were also significant rates of post-operative respiratory complications, even in the intervention groups of these trials and therefore the best rescue method for post-operative respiratory failure remains important.

The evidence for rescue non-invasive ventilation in the peri operative setting is limited. A previous trial using CPAP for post-operative hypoxaemia was stopped early as CPAP reduced the need for intubation.¹⁷ This trial had significantly lower requirements for intubation (1% CPAP vs 10% conventional oxygen therapy) than the current trial (33.1% in the NIV group vs 45.5% in the standard oxygen group). There are significant differences in the studies. In the Squadron trial¹⁷, CPAP was applied following a screening test for hypoxaemia one hour after surgery without clinical signs of respiratory failure. This trial was therefore perhaps more akin to selected prophylaxis than treatment of established respiratory failure. The CPAP trial also excluded 83% of screened patients, in particular patients were excluded if they effectively had any cardiorespiratory disease, infection or were having an emergency procedure. It is perhaps not surprising the event rate was low. In the current trial the intubation rate, at least in the control group, was similar to two previous trials enrolling hypoxic respiratory failure patients.^{13,18} These trials both enrolled largely medical patients with more severe hypoxaemia than in this post-operative trial. Despite similarities, these trials had contrasting results. The earlier trial by Ferrer et al¹⁸ reported a reduced intubation rate in the non-invasive ventilation group, while the trial by Frat et al¹³ did not show any difference. The pathology in these trials was slightly different and could explain the difference in outcomes. The predominant respiratory failure cause in the medical patients was pneumonia, but the Ferrer trial also included significant numbers of patients with pulmonary oedema and immunocompromise, groups who may respond better to non-invasive ventilation. The pathology in the surgical population was mainly atelectasis which again may be more responsive to non-invasive ventilation and could explain the success of the intervention.

Another consideration was the non-invasive settings and dose delivered. It has been suggested the benefit of non-invasive ventilation may be nullified, and the patient returns to the pre non-invasive state, if poorly delivered or interrupted.¹⁰ In this post-operative trial the average duration of non-invasive ventilation was just 7.4 (± 4.9) hours in the first 24 hours. This duration was less than the intervention in several of the successful post-operative prophylaxis trials.^{16,17} Although the intervention in this trial was successful, the question arises; had the duration been longer would the intervention have been even more effective? In this study, there were no difference in the delivery of the intervention between those who failed and those who were successful with non-invasive ventilation.

Lastly, it is worth noting in the multivariate analysis that patients who required re intubation had higher SAP scores, were more likely to be ventilated for longer post



surgery, had more secretions, lower pH and a worse PaO₂/FiO₂. Higher disease severity and more severe hypoxaemia have previously been identified as risk factors for failure of non-invasive ventilation¹⁰. Given the reintubation rate of 33.1% in the intervention group, perhaps these risks should be included when selecting or excluding patients for non-invasive ventilation in future trials.

Where this sits in the body of evidence

In a randomised, controlled, unblinded study 209 patients who developed severe hypoxemia after major elective abdominal surgery were randomly assigned to receive oxygen (n=104) or oxygen plus CPAP (n=105). Patients who received CPAP had a lower intubation rate (1% vs 10%; RR, 0.099; 95% CI, 0.01 to 0.76; P=0.005;) and had a lower occurrence rate of pneumonia (2% vs 10%; RR, 0.19; 95% CI, 0.04 to 0.88; P=0.02), infection (3% vs 10%; RR, 0.27; 95% CI, 0.07 to 0.94; P=0.03), and sepsis (2% vs 9%; RR, 0.22; 95% CI, 0.04 to 0.99; P=0.03). CPAP patients also spent fewer days in the intensive care unit, 1.4 vs 2.6; P=0.09. There was no difference in length of hospital stay or mortality.¹⁷

In a randomised single-centre trial, 50 patients post-elective replacement of the thoracoabdominal aorta were extubated to either continuous CPAP for 12 to 24 hours at an airway pressure of 10 cmH₂O or to standard treatment, including intermittent CPAP (10 cm H₂O for 10 min) every 4 hours. CPAP was applied for a mean (±SD) duration of 23 ± 3 hours and was associated with fewer pulmonary complications (PaO₂/FiO₂ <100 mm Hg, atelectasis, pneumonia, and reintubation rate) compared to the control group (7 of 25 patients vs 24 of 25 subjects, respectively; P=0.019). While there was no difference in ICU length of stay, the mean hospital length of stay was shorter with CPAP therapy (22±2 vs 34± 5 days, respectively; P=0.048).¹⁶

In a single-centre randomised trial, 500 patients post-elective cardiac surgery were allocated to standard treatment, including 10 minutes of intermittent nasal CPAP at 10 cmH₂O every 4 hours or prophylactic nasal CPAP at an airway pressure of 10 cmH₂O for at least 6 hours. Prophylactic CPAP significantly improved arterial oxygenation (PaO₂/FiO₂) without altering heart rate and mean arterial blood pressure. Pulmonary complications, including hypoxemia, pneumonia, and reintubation rate, were reduced in patients in the interventional group compared to controls (12 of 232 patients vs 25 of 236 patients, respectively; P=0.03). The readmission rate to ICU was significantly lower in CPAP-treated patients (7 of 232 patients vs 14 of 236 patients, respectively; P=0.03).¹⁵

In the multi-center, randomised, noninferiority BiPOP Trial, 830 cardiothoracic surgery patients, deemed high risk for respiratory failure after extubation, were randomly assigned to HFNO or BiPAP. HFNO was not inferior to BiPAP; the treatment failed in 21.0% of the HFNO group and 21.9% of the BiPAP group (absolute difference, 0.9%; 95% CI, -4.9% to 6.6%; P=0.003). No significant differences were found for ICU mortality



(BiPAP, 5.5% vs HFNO, 6.8%; P=0.66; absolute difference, 1.2%; 95% CI, -2.3% to 4.8%). Skin breakdown was significantly more common with BiPAP after 24 hours.¹⁹

In the multi-centre study FLORALI trial, 310 patients with non-hypercapnic acute hypoxemic respiratory failure and a PaO₂/FiO₂ ratio < 300 mm Hg, were randomised to HFNO, standard oxygen therapy, or non-invasive positive-pressure ventilation. The intubation rate (primary outcome) was 38% in the HFNO group, 47% in the standard group, and 50% in the non-invasive ventilation group (P=0.18). The number of ventilator-free days at day 28 was significantly higher in the HFNO group (24±8 days, vs 22±10 in the standard-oxygen group and 19±12 in the HFNO therapy group; P=0.02). The hazard ratio for death at 90 days was 2.01 (95% CI, 1.01 to 3.99) with standard oxygen versus HFNO (P=0.046) and 2.50 (95% CI, 1.31 to 4.78) with HFNO therapy versus HFNO (P=0.006).¹³

In a multi-centre randomised trial 105 patients with acute non-hypercapnic hypoxemic respiratory failure (PaO₂ <60 mm Hg or saturations <90% breathing 50% oxygen), were randomly allocated within 24 hours of fulfilling inclusion criteria to non-invasive ventilation (n=51) or high-concentration oxygen therapy (n=54). The primary end-point was the reduction in intubation rate. Both groups had similar characteristics. Compared with oxygen therapy, non-invasive ventilation decreased the need for intubation (25% vs 52%, P=0.010), the incidence of septic shock (12% vs 31%, P=0.028), intensive care unit mortality (18% vs 39%, P=0.028) and increased the cumulative 90-day survival (p=0.025). The improvement of arterial hypoxemia and tachypnoea was higher in the non-invasive ventilation group with time (P=0.029 each).¹⁸

Should we implement this into our practice?

Yes. Patients with hypoxaemia post-abdominal surgery are candidates to receive non-invasive ventilation. Further work will help define the relative roles of non-invasive ventilation and high flow nasal oxygen in this group.

References

1. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Tarsicio Uribe-Leitz, Tarsicio Uribe-Leitz T et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet* 2015; 385: S11.
2. The International Surgical Outcomes Study group. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. *BJA* 2016; 117 (5): 601–9.



3. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of post-operative complications. *Annals of surgery* 2005; 242(3): 326-43.
4. Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012; 380: 1059–65.
5. Richardson J & Sabanathan S. Prevention of respiratory complications after abdominal surgery. *Thorax* 1997;52(Suppl 3):S35–S40.
6. Ireland CJ, Chapman TM, Mathew SF, Herbison GP, Zacharias M. Continuous positive airway pressure (CPAP) during the post-operative period for prevention of post-operative morbidity and mortality following major abdominal surgery. *The Cochrane database of systematic reviews* 2014; 8: CD008930.
7. Serpa Neto A, Hemmes SN, Barbas CS, Beiderlinden M, Fernandez-Bustamante A, Futier E et al; PROVE Network Investigators. Incidence of mortality and morbidity related to post-operative lung injury in patients who have undergone abdominal or thoracic surgery: a systematic review and meta-analysis. *Lancet Respir Med*. 2014;2(12): 1007-1015.
8. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. *Lancet*. 2009; 374(9685):250-259.
9. Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apezteguía C, González M et al. non-invasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med*. 2004;350(24):2452-2460.
10. Brochard L, Lefebvre JC, Cordioli RL, Akoumianaki E & Richard JCM. non-invasive Ventilation for Patients with Hypoxemic Acute Respiratory Failure. *Semin Respir Crit Care Med* 2014;35:492–500.
11. Faria DA, da Silva EM, Atallah ÁN & Vital FM. non-invasive positive pressure ventilation for acute respiratory failure following upper abdominal surgery. *Cochrane Database Syst Rev*. 2015;(10):CD009134.
12. Mascheroni D, Kolobow T, Fumagalli R, Moretti MP, Chen V, Buckhold D. Acute respiratory failure following pharmacologically induced hyperventilation: an experimental animal study. *Intensive Care Med* 1988;15(1):8–14.
13. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbetet S al; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372(23): 2185-2196.
14. Thille A, Contou D, Fragnoli C, Córdoba-Izquierdo A, Boissier F & Brun-Buisson C. Non-invasive ventilation for acute hypoxemic respiratory failure: intubation rate and risk factors. *Critical Care* 2013 17:R269.
15. Zarbock A, Mueller E, Netzer S, Gabriel A, Feindt P & Kindgen-Milles D. Prophylactic nasal continuous positive airway pressure following cardiac surgery protects from



post-operative pulmonary complications: a prospective, randomised, controlled trial in 500 patients. *Chest* 2009; 135: 1252–9

16. Kindgen-Milles D, Muller E, Buhl R, Böhner H, Ritter D, Sandmann W et al. Nasal-continuous positive airway pressure reduces pulmonary morbidity and length of hospital stay following thoracoabdominal aortic surgery. *Chest* 2005; 128: 821–8.
17. Squadrone V, Cocha M, Cerutti E, Schellino MM, Biolino P, Occella P et al. Continuous positive airway pressure for treatment of post-operative hypoxemia: a randomised controlled trial. *J Am Med Assoc* 2005; 293: 589–95.
18. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A. non-invasive ventilation in severe hypoxemic respiratory failure: a randomised clinical trial. *AmJ Respir Crit CareMed* 2003;168(12): 1438–1444.
19. Stéphan F, Barrucand B, Petit P, Rézaiguia-Delclaux S, Médard A, Delannoy B, et al. High-Flow Nasal Oxygen vs non-invasive Positive Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery: A randomised Clinical Trial. *JAMA*. 2015;313(23):2331-9.

HELMET NIV

Patel B, Wolfe K, Pohlman A, Hall J & Kreiss, J. Effect of non-invasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients with Acute Respiratory Distress Syndrome, A Randomised Control Trial, JAMA 2016; 315(22):2435-41

Introduction

Non-invasive ventilation (NIV) is the established initial therapy for hypercapnic respiratory failure in chronic obstructive pulmonary disease (COPD);¹ reducing mortality and the requirement for endotracheal intubation with its attendant risks of delirium, healthcare-associated pneumonia and ICU-acquired weakness. Its role in acute hypoxaemic respiratory failure (AHRF) is less clear, with some evidence of benefit with NIV or Continuous Positive Airways Pressure (CPAP) in cardiogenic pulmonary oedema² and immunocompromised³ critically-ill patients. Potential limitations with NIV include patient compliance, damage to pressure areas and the inability to deliver desired support due to air leak. Treatment failure with the requirement for emergent tracheal intubation is a high-risk event.⁴

NIV may be delivered by a face or nasal mask, mouthpiece or helmet. The helmet is a clear plastic hood sealed by a soft neck collar. It may allow higher inflation pressures with less leakage and more comfort than a traditional mask. This trial compared helmet and facemask delivered NIV in patients meeting ARDS criteria.

Study synopsis

This was a single-centre randomised controlled trial from the medical ICU of the University of Chicago (USA). Eligible patients met the Berlin criteria for ARDS⁵ and had received 8 hours of face mask NIV via a Phillips Respironics V60 NIV ventilator. Ethical approval and individual consent (patient or surrogate) were obtained. Randomisation was blinded and by computer-generated blocks of 4 to 8 to keep group sizes similar. Patients randomised to the intervention were fitted with a helmet connected to an ICU ventilator (Engström Carestation, GE medical) delivering Pressure Support or CPAP at an inspiratory flow rate of >100 l/min. Those allocated to the control group continued treatment with facemask NIV via a Phillips Respironics V60 NIV ventilator

Positive end-expiratory pressure (PEEP), inspiratory pressure and FiO₂ were titrated in both groups targeting SpO₂ 90%, FiO₂ <0.60, respiratory rate <25/min and decreased respiratory muscle use. In clinically improving patients NIV support was reduced and removed if FiO₂ was <0.5 without PEEP. Endotracheal intubation was suggested at defined criteria (seizures, Glasgow Coma Scale score <8, SpO₂<88%, pH<7.2, respiratory rate >35, excessive secretions, device intolerance, vomiting or airway bleeding).



Thereafter, a lung-protective ventilatory strategy was mandated (6 ml/kg tidal volume, titrated PEEP, and daily sedation breaks).

The proportion of patients requiring intubation was the primary endpoint; exploratory secondary outcomes included ventilation-free days, length of hospital stay and 90-day mortality. The planned enrolment of 206 patients gave 80% power (2 sided $\alpha=0.05$) to detect a 20% absolute reduction in the anticipated 50% control group intubation rate. 740 hypoxaemic patients receiving NIV in ICU were screened over 3 years. 657 (89%) were excluded, 456 as they received NIV for less than the 8 hours required. Other exclusion criteria included a do-not-intubate order (85 patients); hypercapnic respiratory failure (40 patients); consent refusal or research staff unavailability (56 patients) and upper airway obstruction (9 patients).

The pre-specified criteria for primary endpoint efficacy was met at the first planned analysis of 70 patients. Despite this, the trial continued, only for the Data and Safety Monitoring Board (DSMB) to later recommended ceasing recruitment due to safety concerns for the control group. Eighty-three patients had been randomised, 44 to the helmet group and 39 to face mask group; all patients were included in the analysis. Baseline characteristics were similar. Median age was 60 years old, 60% were black, 50% immuno-compromised (transplant or cancer related). Numerically more patients in the helmet group had a diagnosis of pneumonia (52% vs 36%). Median APACHE II scores were similar (25 / 26) and baseline PaO₂:FiO₂ was 118 / 144 mm Hg in the helmet / face mask groups, respectively.

Post randomisation patients received NIV for a median of 20 hours (helmet) and 26 hours (face mask). On area-under-curve analysis the helmet group had higher median PEEP levels (8 vs 5.1 cmH₂O; P=0.006); a lower median FiO₂ (0.5 vs 0.6; P=0.02); and lower levels of pressure support (8 vs 11.2 cmH₂O; P<0.001). Median respiratory rate fell significantly in the helmet group (24.5 vs 27.7 /min; P<0.001) but not the facemask group (29.1 vs 28.3 /min; P=0.21).

Endotracheal intubation rate was significantly reduced in the helmet group (primary outcome, rate 18.2% vs 61.5%, absolute difference 43.3%; 95% CI, 24.3 to 62.4%; P<0.001) and remained significant when adjusted for APACHE II score. Intubation was most frequently for respiratory reasons in the facemask group (83%) and neurological reasons in the helmet group (63%). Secondary outcomes also favoured the helmet group. 90-day mortality was reduced (34.1% vs 56.4%; absolute difference, 22.3%; 95% CI 1.4 to 43.3%; P=0.02); there were fewer ventilation days and days in ICU. Hospital length of stay was not significantly reduced (median 10.1 vs 15.2 days; P=0.16). There was no difference in adverse event rates: 3 patients in each group developed skin ulceration and 2 helmets suffered 'brief deflation'.



Study critique

This study was the first to directly compare the helmet and facemask interfaces for NIV and adds significantly to the current knowledge surrounding non-invasive ventilation in acute respiratory failure. The trial was well conducted with effective group separation and complete follow-up of those randomised. Only study patients could access the helmet so any perception of benefit was not a barrier to future recruitment (important in an unblinded study). Ventilatory strategies were standardised before and after intubation and the in-depth analyses of respiratory variables gives credence to proposing a beneficial effect of increased PEEP. However, several factors warrant consideration.

The helmet was used with a more sophisticated ventilator equipped with a separate expiratory limb and able to deliver the higher inspiratory flow rates, rapid pressurisation and sensitive detection of the onset of expiration required. It would have been preferable to use this ventilator in both groups as it may have contributed to the preferential delivery of ventilation in the helmet group, who received higher PEEP levels and lower pressure support (and hence lower driving pressures) and a lower FiO₂, all of which may be advantageous in ARDS.⁶

89% of screened patients were excluded, the majority of which because they did not complete 8 hours of facemask NIV. The high exclusion rate may limit generalisation and also contributed to slow recruitment - extrapolation suggests 7 years may have been needed to achieve the planned sample size. There were 6 amended trial protocols published with markedly different entry criteria to the trial; the first planned to recruit patients at the time of intubation and extubate the intervention group to helmet-NIV. Several required the presence of shock which was only present in 21 patients in the final study. The published results do, however, relate to a more homogenous group of patients receiving NIV and meeting the Berlin ARDS criteria.

Treating clinicians were necessarily unblinded. There were preset criteria for endotracheal intubation, but a clinician decision was still required; for example, whether to intubate or further increase PEEP if hypoxaemic. The helmet group was mainly intubated for neurological deterioration, which may suggest a late stage of critical illness or CO₂ narcosis (CO₂ levels were unfortunately not reported). The helmet seemed to facilitate tolerance of higher levels of support, but a primary outcome unsusceptible to bias (such as meeting preset criteria for treatment failure) may have been preferable.

Recruitment was halted early due to DSMB safety concerns after the publication of a study suggesting face mask NIV was inferior to high-flow nasal oxygen.⁷ Interim analysis had shown the primary endpoint was likely to remain significant if the study proceeded. However, at this stage the 'headline' secondary endpoint of reduced 90-day mortality had a fragility index of 1; i.e. if one more helmet group patient had died significance



would have been lost.⁸ Halting trials early has been shown to over-estimate treatment effects and is ethically questionable when the treatment of concern is in common use.⁹

The primary endpoint of avoidance of endotracheal intubation is not a validated assurance of improved patient outcome in AHRF; with especial concern regarding increased mortality in those severely hypoxaemic or requiring intubation after prolonged NIV.^{4,10,11} Although NIV may well reduce rates of healthcare-associated infections, delirium and ICU-acquired weakness;¹² endotracheal intubation facilitates secretion clearance and control of tidal volume, offers airway protection and allows a reduction of cardio-respiratory work through analgesia and sedation. Of note, the 56.4% mortality rate in the face mask group compares poorly with the overall mortality of 36% in a recent ARDS trial of intubated patients with worse starting PaO₂:FiO₂.¹³

As this was a single-centre unblinded study with a high exclusion rate, clinically uncertain primary outcome and fragile mortality endpoint the investigators are correct to state a multi-centre trial is required to attempt to replicate their findings.

Where this sits in the body of evidence

There is a paucity of modern randomised trials comparing NIV interfaces or testing NIV against endotracheal intubation in AHRF. In 2013 the Cochrane Collaboration systematically reviewed 32 randomised controlled trials with 2916 participants comparing the addition of NIV (including CPAP) to standard medical care in patients with acute cardiogenic pulmonary oedema.² NIV significantly reduced in-hospital mortality (RR, 0.66; 95% CI 0.48 to 0.89; NNT 14) and endotracheal intubation rate (RR, 0.52; 95% CI, 0.36 to 0.75; NNT 8) with no effect on hospital length of stay or rate of myocardial infarction. The mortality benefit was strongest with CPAP.

Antonelli et al in 1995 randomised 64 patients with AHRF to conventional mechanical ventilation or face mask NIV.¹⁴ There was no difference in oxygenation or in-hospital mortality. The study is of limited applicability due to the use of high tidal volumes (10 ml/kg) in the mechanical ventilation group.

Hilbert et al randomised 52 immuno-compromised patients in 1998 to face mask NIV or oxygen therapy in a single French ICU.³ The NIV group had reduced ICU mortality (38% vs 69%; P=0.03) and intubation rate (46% vs 77%; P=0.03). Following publication NIV became the treatment of choice in this patient group; however, concerns were raised regarding the high control-group mortality and requirement for intubation at a PaO₂:FiO₂ of <85 mm Hg.¹⁵

In a multi-centre French/ Belgian follow up study, Lemiale and colleagues randomised 374 immuno-compromised patients with early AHRF to receive oxygen therapy with or without intermittent NIV.¹⁵ Baseline median PaO₂:FiO₂ was 156 mm Hg (NIV group,

n=191) vs 130 mm Hg (oxygen therapy group, n=183). There was no difference in either the primary outcome of 28-day mortality (NIV, 24.1% vs oxygen therapy, 27.3%; P=0.47) or secondary outcomes including intubation rate. High flow nasal oxygen was extensively used (141 patients, including 44% of the oxygen group) which may have diluted any NIV treatment effect.

Antonelli et al in 2000 randomised 40 post solid organ transplantation patients with AHRF to face mask NIV or Venturi mask oxygen.¹⁶ Baseline mean PaO₂:FiO₂ ratio was 129 mm Hg in both groups. NIV patients had lower rates of intubation (20% vs 70%; P=0.002), complications, length of stay and ICU mortality (20% vs 50%; P=0.05). Hospital mortality did not differ. The authors suggest invasive ventilation may be especially deleterious in this setting.

Ferrer et al randomised 105 patients in 3 Spanish ICUs with undifferentiated AHRF to face mask NIV or Venturi mask oxygen.¹⁷ Baseline mean PaO₂:FiO₂ ratio was 102 and 103 mm Hg, respectively. The NIV group had decreased need for endotracheal intubation (by preset criteria, primary endpoint) (25% vs 52%; P=0.01) and ICU mortality (18 vs 39%; P=0.028). Cardiogenic pulmonary oedema (29% of patients) was a predictor of NIV success and survival; meeting ARDS criteria was strongly associated with a poor outcome on multivariate analysis (14% of cohort, adjusted odds ratio for intubation 28.5; 95% CI, 3.2 to 250).

In 2006 Demoule et al prospectively evaluated ventilatory practice and outcome in 70 French ICUs over a 3 day period.⁴ 524 patients with AHRF (n=299) or cardiogenic pulmonary oedema (CPE) / COPD (n=225) were included. Overall, use of NIV was an independent predictor of survival. 54 out of 90 AHRF NIV patients required intubation which was an independent predictor of mortality (OR, 3.24; 95% CI, 1.61 to 6.53).

Correa et al prospectively studied AHRF patients receiving NIV in a Brazilian medical ICU.¹⁰ 26/80 (30.6%) 'failed' NIV requiring intubation. Logistic regression predictors of NIV failure were younger age and higher APACHE II score. NIV failure was associated with higher ICU mortality (OR 4.64; 95 % CI, 1.52 to 14.18; P= 0.007) and longer hospital stay. The NIV success rate was high, possibly due to moderate baseline hypoxia (mean PaO₂:FiO₂ > 270 mm Hg).

The use of HFNO (50 l/min) resulted in improved outcomes when compared with face mask NIV and standard oxygen therapy in 313 ICU patients in a multi-centre French / Belgian randomised controlled trial.⁷ The odds ratio for unadjusted 90-day mortality was significantly higher for both NIV (2.50; 95% CI, 1.31 to 4.78) and standard therapy (OR, 2.01; 95% CI, 1.01 to 3.99), remaining significant when adjusted for SAPS II score and cardiac failure. The primary endpoint of endotracheal intubation (high flow oxygen 38%, standard therapy 47%, NIV 50%, p=0.18/0.19 by log rank test) was only significant in the



subgroup with baseline PaO₂:FiO₂ ratio <200 mm Hg. This was the study referenced by the DSMB when ceasing recruitment to the Helmet-NIV trial.

In a pre-specified secondary analysis the investigators of the descriptive LUNG-SAFE study analysed data for the 436 patients from 209 ICUs who received non-invasive ventilation on the first 2 consecutive days they fulfilled Berlin ARDS criteria.¹¹ No data was collected on the interface (mask or helmet) used, 28% received CPAP and 72% pressure-assisted ventilation. The 131 (37.5%) "failed NIV" patients who subsequently received invasive ventilation had a higher ICU mortality (42.7% vs 10.6%, P<0.001). NIV patients tended to have lower PEEP levels and higher tidal volumes and respiratory rates. Whilst crude mortality rates did not differ, Cox regression analysis suggested NIV was an independent predictor of ICU (but not hospital) mortality (HR 1.45; 95% CI, 1.16 to 1.81). Propensity matching of individual NIV / invasively ventilated patients suggested a higher mortality in NIV patients with baseline PaO₂:FiO₂ <150 mm Hg.

Should we choose the helmet interface over the facemask interface for non-invasive ventilation in acute respiratory failure?

Possibly. Whilst awaiting multi-centre studies the helmet device (or high flow nasal oxygen) could be considered as an alternative to facemask NIV in AHRF. The safety of NIV in this population in general remains unproven.

References

1. Lightowler JV, Wedzicha JA, Elliott MW, Ram FSF. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *BMJ* 2003;326(7382):185.
2. Vital FMR, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. *Cochrane Database Syst Rev* 2013;(5):CD005351.
3. Hilbert G, Gruson D, Vargas F, et al. non-invasive Ventilation in Immunosuppressed Patients with Pulmonary Infiltrates, Fever, and Acute Respiratory Failure. *N Engl J Med* 2001;344(7):481–7.
4. Demoule A, Girou E, Richard J-C, Taille S, Brochard L. Benefits and risks of success or failure of non-invasive ventilation. *Intensive Care Med* 2006;32(11):1756–65.
5. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307(23):2526–33.



6. Ridler N, Plumb J, Grocott M. Oxygen Therapy in Critical Illness: Friend or Foe? A Review of Oxygen Therapy in Selected Acute Illnesses. *J Intensive Care Soc* 2014;15(3):190–8.
7. Frat J-P, Thille AW, Mercat A, et al. High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure. *N Engl J Med* 2015;372(23):2185–96.
8. Walsh M, Srinathan SK, McAuley DF, et al. The statistical significance of randomised controlled trial results is frequently fragile: a case for a Fragility Index. *J Clin Epidemiol* 2014;67(6):622–8.
9. Bassler D, Briel M, Montori VM, et al. Stopping randomised trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *JAMA* 2010;303(12):1180–7.
10. Corrêa TD, Sanches PR, de Moraes LC, Scarin FC, Silva E, Barbas CSV. Performance of non-invasive ventilation in acute respiratory failure in critically ill patients: a prospective, observational, cohort study. *BMC Pulm Med* [Internet] 2015 [cited 2016 Oct 16];15(1). Available from: <http://bmcpulmed.biomedcentral.com/articles/10.1186/s12890-015-0139-3>
11. Bellani G, Laffey JG, Pham T, et al. Non-invasive Ventilation of Patients with ARDS: Insights from the LUNG SAFE Study. *Am J Respir Crit Care Med* [Internet] 2016 [cited 2016 Oct 30]; Available from: <http://www.atsjournals.org/doi/10.1164/rccm.201606-1306OC>
12. Girou E, Schortgen F, Delclaux C, et al. Association of non-invasive ventilation with nosocomial infections and survival in critically ill patients. *JAMA* 2000;284(18):2361–7.
13. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome. *N Engl J Med* 2010;363(12):1107–16.
14. Antonelli M, Conti G, Rocco M, et al. A Comparison of non-invasive Positive-Pressure Ventilation and Conventional Mechanical Ventilation in Patients with Acute Respiratory Failure. *N Engl J Med* 1998;339(7):429–35.
15. Lemiale V, Mokart D, Resche-Rigon M, et al. Effect of non-invasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure: A randomised Clinical Trial. *JAMA* 2015;314(16):1711.
16. Antonelli M, Conti G, Bui M, et al. non-invasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomised trial. *JAMA* 2000;283(2):235–41.
17. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A. non-invasive Ventilation in Severe Hypoxemic Respiratory Failure: A randomised Clinical Trial. *Am J Respir Crit Care Med* 2003;168(12):1438–44.



LIPS-A

Kor D, Carter RE, Park PK, Festic E, Banner-Goodspeed VM, Hinds R, et al. Effect of Aspirin on Development of ARDS in At-Risk Patients Presenting to the Emergency Department. The LIPS-A randomised Clinical Trial. JAMA 2016;315(22):2406-2414

Introduction

Acute respiratory distress syndrome is a form of non-cardiogenic pulmonary oedema secondary to an inflammatory alveolar insult, which may be pulmonary (e.g. pneumonia) or non-pulmonary (e.g. acute pancreatitis) in origin. It is described by the Berlin definition,¹ and, as a syndrome, is a binary determination – if the definition is met, the condition is present, if not, it is absent.

ARDS remains a common problem, with the global LUNGSAFE observational study reporting 10.4% of ICU patients and 23.4% of mechanically ventilated patients suffering with this form of respiratory failure.² For countries with less developed healthcare systems ARDS remains a major problem; data from Rwanda suggest up to 4% of all hospital admissions may develop this condition.³ Recognition of the syndrome is generally limited, with just 64% of all cases identified, although this improves with worsening severity – mild ARDS (51%), moderate ARDS (65%) and severe ARDS (78.5%) ($P < 0.001$).² In-hospital mortality remains high at 40%, which again increases with worsening hypoxia - mild ARDS (35%), moderate ARDS (40%) and severe ARDS (46%) ($P < 0.001$).²

At present, there is no specific therapy which modifies the pathophysiological mechanisms leading to the clinical state of ARDS. The only successful interventions work through the avoidance or amelioration of ventilator-induced lung injury, namely early low tidal volume ventilation, neuromuscular blockade, prone positioning and possibly extra-corporeal membrane oxygenation, although this remains to be adequately tested.⁴ Platelet activity is a core component of the inflammatory response in ARDS, contributing to thrombosis, leukocyte recruitment and activation, neutrophil extracellular trap formation, vascular permeability and oedema generation. Therefore, anti-platelet therapy could potentially lessen this process.⁵

Study synopsis

The LIPS-A trial was a phase IIb multi-centre, blinded, placebo-controlled, parallel group randomised trial in patients at risk for the development of ARDS.⁶ The trial objective was to assess whether aspirin reduced the development of ARDS in emergency department patients at risk for this condition, as determined by a LIPS score > 4 . The LIPS score is a validated tool for predicting the onset of ARDS and consists of various predisposing conditions, risk modifiers, and respiratory physiology variables.⁷



Relevant exclusion factors included established ARDS, existing bilateral pulmonary infiltrates, current anti-platelet therapy and high bleeding risk. Possible confounding interventions were standardised using the Checklist for Lung Injury Prevention (CLIP),⁸ including the use of protective ventilation (Vt 6 to 8 ml/kg predicted body weight & plateau pressure <30 cmH₂O), aspiration precautions, infection control, plus fluid (use of a modified FACCT protocol aiming to minimise fluid overload) and transfusion practice (haemoglobin level maintained > 70 g/dL, with avoidance of platelet and plasma transfusions for minimally invasive procedures unless actively bleeding).

Randomisation was performed centrally in a 1:1 ratio using Medidata Balance, a commercial cloud-based trial management system, with centre stratification. Participants and investigators were blinded to group allocation. Adult patients were allocated to either aspirin (325 mg loading dose followed by 81 mg per day, n=195) or identical placebo (n=195), with the study drug to be administered within 24 hours of presentation to hospital. The study drug was continued for up to seven days, hospital discharge or death.

The primary outcome was the development of ARDS, as per the Berlin Definition, within seven days of hospitalisation. This determination was limited to patients receiving invasive mechanical ventilation. Secondary outcomes included ventilator-free days to day 28, ICU and hospital lengths of stay, and mortality at 28 days and one year.

One hundred and ninety seven patients per group were required to identify a 10 percentage point decrease in the development of ARDS, from 18% to 8%, at a two-sided significance level of 10% (which decreased to 9% after interim analyses) and a power of 90%. Two hundred patients per group were recruited to allow for attrition. Secondary endpoints were considered exploratory as adjustment for multiple testing was not performed. The initial intention-to-treat primary analysis was changed to a modified intention-to-treat, allowing for withdrawal of consent and ineligibility. "Go-No-Go" recommendations for progression to a phase III trial, dependent on the results of this phase IIb trial, were also set.

7,673 patients were screened at 16 American academic hospitals between 2012 and 2014, with 400 patients being randomised. The majority of those excluded were already receiving an anti-platelet agent (42%), unable to consent within 12 hours (18%), had bilateral pulmonary infiltrates (16%), had suspected bleeding (14%) or were not "committed to full life support" (9%).

Ten patients were excluded due to withdrawal of consent (n=7) or inclusion criteria not being met (n=3), leaving 195 in each group. Groups were similar at baseline, with a typical patient being a 57 year old white male, with suspected sepsis. Approximately 60% had possible pneumonia. 95% of the intervention group received at least one dose



of aspirin, while 97% of the control group received at least one dose of placebo, with no difference in the median number of study drug doses between groups. The intervention was delivered after randomisation at a median time of approximately 12.5 hours in both groups.

There was no difference in the primary outcome between groups, with ARDS developing in 10.3% (n=20) of the aspirin group and 8.7% (n=17) of the placebo group (site adjusted OR, 1.24; 92.6% CI, 0.67 to 2.31). Similarly, there were no significant differences in any of the secondary endpoints (aspirin vs placebo), including survival at both 28 days (90% vs 90%; HR, 1.03; 90% CI, 0.60 to 1.79; log rank P=0.092) and one year, or adverse events, including bleeding. Those receiving aspirin were more likely to be admitted to ICU (59% vs 50%; OR, 1.41; 90% CI, 1.02 to 1.99; P=0.08).

Study critique

As a large contributor to critical care morbidity and mortality, ARDS continues to attract attention from the research community. This medium sized randomised controlled trial failed to identify a beneficial effect from aspirin in patients at risk for ARDS. As a condition with a high prevalence and associated significant morbidity and mortality, ARDS is a high value target to critical care researchers. To date, over 150 randomised controlled trials involving a spectrum of interventions, either prophylactic or therapeutic, have been undertaken.³⁰ Any potential prophylactic therapy would likely be widely implemented. Presently, only a handful of trials have reported an advantageous effect on the primary outcome. This finding forces the question as to why researchers have been so unsuccessful in addressing this condition.

One key point repeatedly overlooked in ARDS trial design is the limited accuracy of the defined syndrome for the true pathology of diffuse alveolar damage. Across a range of open lung biopsy⁹⁻¹² and post mortem studies,¹³⁻¹⁶ the incidence of diffuse alveolar damage, in patients identified as having ARDS by either the American-European Consensus Conference definition or the Berlin definition, is approximately just 50%. This equates to potentially every second patient in an ARDS trial which attempts to modify the inflammatory process of alveolar injury not actually having the therapeutic target present, with a clear implication of a resulting underpowered trial. Those without diffuse alveolar damage suffer a wide range of unrelated conditions, including pulmonary embolism, pulmonary haemorrhage, pulmonary fibrosis, lung cancer, chronic obstructive pulmonary disease and atelectasis.¹⁶

The ARDS trials to date which have identified beneficial (or harmful) interventions have either investigated ventilator-induced lung injury^{17,18} or limited inclusion to more severely hypoxaemic ARDS patients,¹⁹ a subgroup with a higher incidence of diffuse alveolar damage. The implication for ongoing pharmacological trials is clear. Whether the definition is fit for research purposes is a question some have raised,^{20,21} but a nettle



few have grasped.

The power calculation could be described as optimistic, with a stated 55% relative risk reduction appearing an overly large effect size to achieve. Ultimately, the incidence of ARDS was numerically higher in the aspirin group, lessening the risk this was an underpowered trial.

With an ARDS incidence of 8.7% in the control group, rather than the expected 18% as stated in the power calculation, the recruited population was of a lower risk than expected. This may have lessened the degree of inflammation present in this cohort and thus reduced the ability of aspirin to modify it.

The Lung Injury Prediction Score is a limited tool. It was initially developed⁷ and subsequently validated²² in different cohorts by the same team of investigators. Although it has excellent negative predictive values (>97%), it has a poor positive predictive value and low positive and negative likelihood ratios. Despite a median LIPS score of 6 in this trial, a value which previously equated to an incidence of ARDS of 15%, the realised incidence of ARDS was only approximately two-thirds of this.²³

The groups did separate with regard to their exposure to aspirin. While the majority of patients did receive at least one dose of the study drug, the median number of doses delivered was low, at just four for the aspirin group and five for the placebo group. Therefore, despite using a dose known to have an anti-inflammatory effect, and which has been associated with an anti-ARDS effect in observational work, there was no meaningful difference in levels of inflammatory markers between groups, raising the question as to whether this dose was sufficient to achieve a biological effect in this specific cohort. Blood levels were not measured, but as there was no suggestion of gastrointestinal failure in the cohort, absorption was presumably not an issue. The intervention was delivered early, within 12 hours of hospitalisation, maximising the opportunity for a beneficial effect, as ARDS typically develops within the first two days of hospitalisation.

Importantly, confounders such as the delivery of invasive mechanical ventilation and fluids were standardised across sites and groups, leaving the intervention as the main difference between groups.

A major problem with the application of any ARDS definition has been the adjudication of the chest radiograph for the presence of bilateral infiltrates consistent with non-cardiogenic pulmonary oedema.²⁴ The trialists, blinded to the group allocation, followed a clear, consistent pathway for this determination. With a requirement for invasive mechanical ventilation, standardised ventilatory settings, and a clear screening process, including radiographic interpretation, the identification of ARDS was optimised within

the aforementioned limits of the Berlin Definition. This is clearly important when the primary outcome is the development of ARDS. Of course, with 50% of patients identified in this way actually suffering from conditions such as atelectasis and not having diffuse alveolar damage, the discussion begins to become circular.

Where this sits in the body of evidence

At present there is little evidence to inform the efficacy of aspirin either for the prevention or treatment of ARDS, with no large randomised controlled trials undertaken. The clinical studies which have been completed to date are observational, reporting associations between aspirin therapy and outcome, but which are limited by residual confounding and are unable to further inform this relationship.

In a single-centre retrospective study including 202 patients with ARDS, aspirin administration, either pre-hospital or in ICU, was associated with reduced ICU mortality (OR 0.38; 95% CI, 0.15 to 0.96; $P=0.04$).²⁵

Kor and colleagues completed a secondary analysis of a cohort study from the USA and Turkey involving 3,855 consecutive adults admitted to hospital with at least one risk factor for ARDS. Those receiving aspirin at the time of hospital admission ($n=976$, 25.3%) were less likely to develop ARDS than those not receiving aspirin (OR, 0.65; 95% CI, 0.46 to 0.90; $P=0.010$).²⁶

In a small, retrospective, two-centre study, Erlich and colleagues analysed data from 161 patients without ARDS at the time of ICU admission, but with a risk factor for its development. Pre-hospital aspirin use ($n=79$, 49%) was associated with a lower incidence of the development of ARDS (12.7% vs 28.0%; OR, 0.37; 95% CI, 0.16 to 0.84; $P=0.02$).²⁶

Mazzeffi and colleagues also completed a retrospective, single-centre study including all 375 patients who had an aortic valve replacement at their institution over a five year period. 181 patients used an anti-platelet agent routinely. The incidence of ARDS did not differ between those who did and did not use anti-platelet agents (5.0 vs 6.7%, respectively; crude OR, 0.725; 99% CI, 0.229 to 2.289; $P=0.47$).²⁷

Wang and colleagues completed a very recent meta-analysis of nine cohort studies examining the effect of antiplatelet therapy on ARDS and mortality in critically ill patients. 14,612 patients were included, with 4,765 patients receiving anti-platelet agents. This therapy was associated with both a reduced incidence of ARDS (OR 0.64; 95% CI, 0.50 to 0.82; $I^2 = 0\%$; $P < 0.001$) and mortality (OR 0.61; 95% CI, 0.52 to 0.71; $I^2 = 0\%$; $P < 0.001$), a finding which was consistent across subgroups.²⁸

Al Harbai and colleagues undertook a post hoc analysis²⁹ of two randomised controlled trials evaluating glycaemic control and nutrition in critical care. Of the 763 patients



included, 20% (n=154) usually took aspirin. This therapy was not associated with a reduction in mortality either in ICU (adjusted OR, 1.18; 95 % CI, 0.69 to 2.02; P=0.55) or in hospital (adjusted OR, 0.95; 95% CI, 0.61 to 1.50; P=0.82), but was associated with increased morbidity, in the form of a higher risk of ICU-acquired severe sepsis (adjusted OR, 1.70; 95% CI, 1.08 to 2.70; P=0.02), increased days of mechanical ventilation (adjusted OR, 2.7; 95% CI, 0.51 to 4.90; P=0.02) and ICU length of stay (adjusted OR, 2.67; 95% CI, 0.38 to 4.96; P=0.02).

The STAR trial (NCT02326350), an ongoing single-centre phase II trial investigating aspirin in patients with ARDS, will further inform this field.

Should we implement this into our practice?

No, aspirin administration did not reduce the incidence of ARDS in an emergency department population at risk for the development of this condition, as identified by the LIPS score.

References

1. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA J Am Med Assoc* 2012;307(23):2526.
2. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016;315(8):788–800.
3. Riviello ED, Kiviri W, Twagirumugabe T, et al. Hospital incidence and outcomes of the acute respiratory distress syndrome using the Kigali modification of the Berlin definition. *Am J Respir Crit Care Med* 2016;193(1):52–9.
4. Mac Sweeney R, McAuley DF. Acute respiratory distress syndrome. *Lancet* 2016;388(10058):2416–30
5. Toner P, McAuley DF, Shyamsundar M. Aspirin as a potential treatment in sepsis or acute respiratory distress syndrome. *Crit Care* 2015;19(1):1–9.
6. Kor DJ, Carter RE, Park PK, et al. Effect of Aspirin on Development of ARDS in At-Risk Patients Presenting to the Emergency Department: The LIPS-A randomised Clinical Trial. *JAMA* 2016;
7. Gajic O, Dabbagh O, Park PK, et al. Early Identification of Patients at Risk of Acute Lung Injury: Evaluation of Lung Injury Prediction Score in a multi-centre Cohort



Study. *Am J Respir Crit Care Med* 2011;183(4):462–70.

8. Litell JM, Gajic O, Sevransky J, Gong M, Murphy DJ. multi-centre consensus development of a checklist for lung injury prevention. *Crit Care* 2012;16(1):1.
9. Kao K-C, Tsai Y-H, Wu Y-K, et al. Open lung biopsy in early-stage acute respiratory distress syndrome. *Crit Care* 2006;10(4):R106.
10. Charbonney E, Robert J, Pache J-C, Chevrolat J-C, Eggimann P. Impact of bedside open lung biopsies on the management of mechanically ventilated immunocompromised patients with acute respiratory distress syndrome of unknown etiology. *J Crit Care* 2009;24(1):122–8.
11. Patel SR, Karpaliotis D, Ayas NT, et al. The role of open-lung biopsy in ARDS. *CHEST J* 2004;125(1):197–202.
12. Guerin C, Bayle F, Leray V, et al. Open lung biopsy in nonresolving ARDS frequently identifies diffuse alveolar damage regardless of the severity stage and may have implications for patient management. *Intensive Care Med* 2014;1–9.
13. Ferguson ND, Frutos-Vivar F, Esteban A, et al. Acute respiratory distress syndrome: Underrecognition by clinicians and diagnostic accuracy of three clinical definitions *. *Crit Care Med* 2005;33(10):2228–34.
14. Esteban A, Fernández-Segoviano P, Frutos-Vivar F, et al. Comparison of Clinical Criteria for the Acute Respiratory Distress Syndrome with Autopsy Findings. *Ann Intern Med* 2004;141(6):440–5.
15. de Hemptinne Q, Rimmelink M, Brimiouille S, Salmon I, Vincent J-L. ARDS : A Clinicopathological Confrontation. *Chest* 2009;135(4):944–9.
16. Thille AW, Esteban A, Fernández-Segoviano P, et al. Comparison of the Berlin Definition for Acute Respiratory Distress Syndrome with Autopsy. *Am J Respir Crit Care Med* 2013;187(7):761–7.
17. The Acute Respiratory Distress Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342(18):1301–8.
18. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome. *N Engl J Med* 2010;363(12):1107–16.
19. Guérin C, Reignier J, Richard J-C, et al. Prone Positioning in Severe Acute Respiratory Distress Syndrome. *N Engl J Med* 2013;368(23):2159–68.
20. Fröhlich S, Murphy N, Boylan JF. ARDS: progress unlikely with non-biological definition. *Br J Anaesth* 2013;111(5):696–9.
21. Cardinal-Fernández P, Esteban A, Thompson BT, Lorente JA. ARDS: Lessons Learned From the Heart. *Chest* 2015;147(1):7–8.



22. Trillo-Alvarez C, Cartin-Ceba R, Kor DJ, et al. Acute lung injury prediction score: derivation and validation in a population-based sample. *Eur Respir J* 2011;37(3):604–9.
23. Mazzeffi M. Pharmacotherapy in acute respiratory distress syndrome—the long and winding road. 2016 2016;8(9):2337–9.
24. Rubenfeld GD, Caldwell E, Granton J, Hudson LD, Matthay MA. Interobserver Variability in Applying a Radiographic Definition for ARDS. *Chest* 1999;116(5):1347–53.
25. Boyle AJ, Di Gangi S, Hamid UI, et al. Aspirin therapy in patients with acute respiratory distress syndrome (ARDS) is associated with reduced intensive care unit mortality: a prospective analysis. *Crit Care* 2015;19(1):1–8.
26. Kor DJ, Erlich J, Gong MN, et al. Association of pre-hospitalization aspirin therapy and acute lung injury: results of a multi-centre international observational study of at-risk patients. *Crit Care Med* 2011;39(11):2393.
27. Mazzeffi M, Kassa W, Gammie J, et al. pre-operative Aspirin Use and Lung Injury After Aortic Valve Replacement Surgery: A Retrospective Cohort Study. *Anesth Analg* 2015;121(2):271–7.
28. Wang L, Li H, Gu X, Wang Z, Liu S, Chen L. Effect of Antiplatelet Therapy on Acute Respiratory Distress Syndrome and Mortality in Critically Ill Patients: A Meta-Analysis. *PloS One* 2016;11(5):e0154754.
29. Al Harbi SA, Tamim HM, Al-Dorzi HM, Sadat M, Arabi YM. Association between aspirin therapy and the outcome in critically ill patients: a nested cohort study. *BMC Pharmacol Toxicol* 2016;17(1):1–7.
30. Tonelli AR, Zein J, Adams J, Ioannidis JP. Effects of Interventions on Survival in Acute Respiratory Distress Syndrome: an Umbrella Review of 159 Published randomised Trials and 29 Meta-analyses. *Intensive Care Med* 2014;40(6):769–787



Oxygen-ICU

Girardis M, Busani S, Damiani E, Donati A, Rinaldi L. Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU randomised Clinical Trial. JAMA 2016;316:1583-89

Introduction

Oxygen is a key determinant of cellular metabolism, with energy released by its oxidation driving ATP production by the mitochondrial electron transport chain. Critical illness is often characterised by a catastrophic failure of oxygen delivery or utilisation, the degree of which correlates with outcome.¹ The administration of additional oxygen is a core therapy in hospitalised patients, however the degree to which hypoxaemia should be corrected has become of interest. Molecular oxygen is highly chemically reactive and directly toxic to most unicellular organisms, reactive oxygen species produced in in-vivo hyperoxic states are especially so. Insights gained from extreme altitude physiology have highlighted the survivability of severe hypoxaemia, consistent with the knowledge that mitochondria function physiologically at a tissue PO₂ of 1-4 kPA.²

Clinical studies have increasingly demonstrated potential harm from oxygen therapy. Direct pulmonary toxicity with interstitial fibrosis and atelectasis has been a driver for developing ventilatory strategies and adjunctive therapies to limit FiO₂ in ARDS.³ Excessive supplemental oxygen has been associated with worse outcomes in acute myocardial infarction, stroke and cardiac arrest; challenging the paradigm of “first give more oxygen”.⁴ This study aimed to test the hypothesis that strictly controlling arterial oxygenation may lead to improved clinical outcomes in critically ill patients.

Study synopsis

The study was an open-label randomised controlled trial conducted over a 2-year period in a single Italian ICU. Eligible patients had an expected length of stay of over 72 hours and no exclusion criteria (pregnancy, age <18 years, readmission, limitation to treatment, immunosuppression, inclusion in another study, decompensated COPD or a PaO₂:FiO₂ <150 mm Hg). Ethical approval and individual consent were obtained; randomisation was concealed and computerised. The control group received oxygen therapy with a minimum FiO₂ of 0.4, targeting a SpO₂ 97% to 100% and allowing a PaO₂ up to 150 mm Hg (20.0 kPa). In the conservative intervention group oxygen was titrated to maintain the PaO₂ between 70 to 100 mm Hg (9.3 kPa to 13.3 kPa) or SpO₂ between 94% to 98%; and discontinued if possible. Management also differed for procedures such as intubation, suction and hospital transfer; control patients received an FiO₂ of 1.0 and intervention patients only received supplemental oxygen if SpO₂ fell below 94%. Arterial blood gas (ABG) testing beyond a daily sample was dictated by clinical need, the treating physician decided on other aspects of care. Time-weighted averages were used



to compare the PaO₂ and FiO₂ values between groups.

The primary outcome measure was ICU mortality, assessed in a modified intention-to-treat (ITT) population comprising those randomised patients with an ICU length of stay over 72 hours and a daily ABG. Pre-specified secondary outcomes included new organ-failures, microbiologically confirmed infections and re-operation in surgical patients. All outcomes were also assessed in a true ITT population. The planned recruitment of 660 patients would have 80% power (2-sided $\alpha=0.05$) to detect a 6% absolute change from the predicted 23% ICU mortality in the control group.

The trial was halted early after an earthquake seriously damaged the hospital and recruitment slowed. At this stage 1045 patients had been screened over a 30-month period. 565 were excluded: 108 were children; 310 expected to stay <3 days; 52 admitted with COPD and 13 severe ARDS; 41 had treatment limitations and 17 were neutropaenic. 480 patients were randomised, all received the intervention, but only 434 patients (216 and 218 in the conservative and conventional oxygen groups, respectively) were included in the modified ITT analysis (35 had <72 hour ICU stay, 9 no daily ABG and 2 withdrew consent.) Baseline characteristics in each group were similar. Median age was 64 years, 57% were male and 62% post-surgery. Median SAPS II score was 38, 67% were mechanically ventilated, 32% had shock, 15% renal failure and 20% hepatic failure.

The conventional group received more oxygen and had higher median time-weighted PaO₂ values (102 mm Hg (IQR 88 to 116) vs 87 mm Hg (IQR 79 to 97), $P < 0.001$). There was no statistically significant excess in PaO₂ values <70 mm Hg with conservative oxygen therapy (median 1 event (IQR 0 to 2) in both groups. ICU mortality was significantly lower in the conservative oxygen group (11.6% vs 20.2%; RR, 0.57, 95% CI, 0.37 to 0.90; $P=0.01$). Hospital mortality was also reduced. There were significant ($P \leq 0.05$) differences in favour of conservative oxygen therapy in 4 of the 13 secondary outcomes presented (new shock, new liver failure, new bacteraemia and ventilation-free hours). There was no significant difference in ICU (or hospital) length of stay or progression of organ failure. Analysing the true ITT population did not significantly change the results.

Study critique

This is a significant addition to the critical care literature. The improved ICU mortality seen with conservative oxygen administration could be consistent with current understanding of critical illness; with little evidence for aggressive over-correction of physiological derangement;¹ but had not been demonstrated in an ICU randomised controlled trial previously. The study was appropriately randomised, had a clear oxygen administration protocol and achieved a statistically significant separation in both delivered oxygen and measured PaO₂ between the two groups. There are, however, several issues to consider if applying this study to current practice.



Bedside nurses and clinicians were aware of the group allocation, delivered FiO_2 and measured PaO_2 values, which could potentially introduce bias but was probably required for safe care. The ability of time-weighted averages to accurately reflect variations in PaO_2 depends on the frequency of ABG sampling which was uncontrolled and unfortunately not reported; conceivably, the separation in oxygenation between the groups could well have been under- or over-stated. SpO_2 is not a reliable alternative as a indicator of PaO_2 due to its vulnerability to changes in oxyhaemoglobin dissociation.

The study was halted early after an earthquake significantly disrupted the infrastructure of the recruiting hospital and it was calculated the study would have taken over 4 years to complete. An unplanned interim analysis at this stage confirmed a positive result for the primary endpoint but this was a fragile result - if 3 more patients in the conservative group had died significance would have been lost. It is notable in this context that 2 patients withdrew consent and were excluded from the analysis. Halting studies early has been shown to potentially exaggerate the treatment effect of the intervention.⁵

The decision to analyse primarily by “modifying” the ITT population is questionable. Patients not remaining for 72 hours in ICU were excluded after randomisation, reportedly to avoid incomplete data collection. This may have aided the evaluation of secondary endpoints but would have compromised the primary outcome assessment if one of the strategies increased early ICU mortality or facilitated early discharge. Of note this modification was not documented in the original trial protocol (electronic supplement) and was unnecessary if the study was adequately powered, as the entry criteria required an expected length of stay over 72 hours. Excluding patients without a daily ABG could also introduce bias if the higher SpO_2 values in the conventional group meant less samples were taken. Reassuringly the authors present the true ITT data in the electronic supplementary material and there are no important outcome differences.

This was not a study of permissive hypoxia, with the conservative group titrated to ‘normal’ targets (SpO_2 94% to 98% and PaO_2 70 to 100 mm Hg). Despite statistically significant separation in oxygenation there was considerable overlap in both target oxygen saturations (97% to 98% was acceptable in both groups) and in the measured time-weighted PaO_2 (shown by an overlap in the reported inter-quartile ranges and graphically in the supplementary data). Increased group separation may have changed outcomes.

It could be argued the trial really examined the safety of liberal oxygen administration; in the conventional arm FiO_2 was not reduced below 0.4 unless the PaO_2 exceeded 150 mm Hg (20 kPa); and 100% oxygen given for procedures and transfers. The study reported the frequency of hypoxic events but did not report the corresponding frequency of hyperoxia; of note, the highest recorded patient median time-weighted



PaO₂ in the conventional group was 220 mm Hg (29.3 kPa). The excess mortality seen in this group may be evidence of harm. It is noteworthy that the target PaO₂ in a recent trial examining the use of neuromuscular blockers in ARDS was 55 - 80 mm Hg.⁶ Future trials may examine true permissive hypoxaemia, or at least balance separating oxygenation between groups whilst avoiding excess hyperoxia.

The patients in the conventional group had numerically higher rates of age, co-morbidities, organ failures and SAPS II score which, although individually non-significant, could conceivably together have impacted on outcome. Lastly, there appear to be two typographical mistakes in the published manuscript, which imply the conventional group had more hypoxaemic ABG results and less new infections, which are contradicted by the given data.

For the above reasons this trial should be replicated in a multi-centre setting with adequate power to identify a mortality benefit of less magnitude than seen in this pilot study.

Where this sits in the body of evidence

Two large retrospective cohort studies suggested a potential harmful association between hyperoxia and ICU outcome.^{7,8} These were countered by publications utilising similar methodologies but applied to the Australian and New Zealand Intensive Care Society (ANZICS) database.⁹⁻¹² Prospective studies in this area are limited to non-ICU studies¹³ a before-and-after ICU trial¹⁴ and a pilot multi-centre ICU study reviewed in this book¹⁵.

In 2008 de Jonge et al reviewed data on 36,307 patients admitted between 1999 and 2006 from the Dutch national intensive care registry.⁷ Regression analysis revealed a 'U' shaped relationship between first-24 hour PaO₂ and in-hospital mortality, which remained after correction for demographics and SAPS II score (PaO₂ ≥16 kPa associated with OR for mortality of 1.23; 95% CI 1.13 to 1.34). Beyond 24 hours a high FiO₂ (but not PaO₂) was a predictor of mortality independent of selected potential confounders including PaO₂:FiO₂ ratio and SAPS II score.

In 2010 the EMShockNet investigators published a retrospective cohort study of 6326 post-cardiac arrest patients admitted to 120 US ICUs from 2001-05.⁸ Overall survival was 44%, 34% with functional independence. Mortality was significantly higher in the hyperoxaemia (PaO₂ ≥300 mm Hg) group than both the 'hypoxia' (PaO₂ ≤60 mm Hg or PaO₂:FiO₂ ≤300 mm Hg) group (63% vs 57%, difference 6%, 95% CI, 3 to 9%; P<0.001); and than the 'normoxaemia' (other PaO₂ values) group (63% vs 45%, difference 18%; 95% CI, 14 to 22%; P<0.001). Oxidative stress following reperfusion was the suggested pathological mechanism. Unfortunately the use of PaO₂:FiO₂ categorised some patients with impaired oxygen transfer as hypoxic despite a normal or high PaO₂. In a subsequent



publication the same authors described a dose-dependent relationship between the highest PaO₂ in the first 24 hours in ICU and in-hospital mortality (6% increase in mortality per 25 mm Hg increase in PaO₂).¹⁶

In contrast Bellomo et al in 2011 applied the same methodology to the ANZICS ICU database and found that when corrected for potential confounders, including FiO₂, hyperoxia was not an independent predictor of mortality in 12,108 post non-traumatic cardiac arrest patients.⁹ This group also separately analyses patients with true hypoxia (PaO₂ ≤ 60mm Hg), which was associated with poor outcomes.

In 2012 Eastwood et al retrospectively extracted first-24 hour oxygenation data from the ANZICS database for 152,680 patients admitted to Australian and New Zealand ICUs from 2000 to 2009.¹⁰ Hyperoxia (PaO₂ >120 mm Hg (16 kPa)) was present in 49.8%. When adjusted for baseline characteristics and illness severity there was no association between raised PaO₂ and in-hospital mortality.

In 2014 the same methodology was used to examine outcomes following cardiac surgery in 83,060 patients identified from the ANZICS database and admitted between 2003 and 2012.¹¹ There was no association between first-24 hour hypoxia and ICU mortality when 'hyperoxic' patients were compared to 'nontoxic'; there was a clinically insignificant (0.1 day) difference in ICU and hospital length of stay that was statistically significant.

In 2012 data on 2,463 mechanically ventilated patients with ischaemic stroke (identified by APACHE III coding) admitted between 2000 and 2009 was extracted from the ANZICS database.¹² Median PaO₂ was 117 mm Hg (IQR 87 to 196 mm Hg). There was no association between recorded first-24 hour PaO₂ levels and clinical outcomes (mortality, length of stay or discharge home).

In 2015 the AVOID investigators randomised 638 patients with suspected acute myocardial infarction (MI) to 8 l/min supplemental oxygen or oxygen only if SpO₂ fell below 94%.¹³ The primary analysis was restricted to 441 patients with confirmed ST-elevation MI. There was a significantly raised mean peak creatinine kinase (but not troponin-T) in the supplemental oxygen group (RR 1.26, 95% CI, 1.05 to 1.52, P=0.01). The supplemental oxygen group also had significantly more dysrhythmias and re-infarctions within hospital (but not by 6 months) and a larger 6-month infarct size in the 127 patients evaluated for this outcome.

In a 2014 before-and-after feasibility study in a single Australian ICU 54 mechanically ventilated adults treated with a conservative oxygen protocol (target SpO₂ 90% to 92%) were compared with 51 prior patients treated at clinician discretion.¹⁴ Whilst separation was achieved with the conservative group having significantly lower SpO₂, PaO₂ and FiO₂ values on time-weighted analysis there was no difference in the chosen primary



outcome of PaO₂:FiO₂. Exploratory secondary outcomes did not suggest harm. The conventional group had been the subject of a previously published observational cohort study by the same authors.¹⁷

In a 2016 multi-centre unblinded pilot study Panwar et al randomised 103 mechanically ventilated ICU patients to a conservative (SpO₂ 88 to 92%) or liberal (SpO₂ ≥96%) oxygenation strategy.¹⁵ Significant group separation was achieved for mean SpO₂, PaO₂ and FiO₂ values measured by area-under-curve analysis (primary endpoints, P<0.001 for all). There was an increase in vasopressor dose and arterial desaturations in the conservative group but no significant differences in any of the other 17 pre-specified secondary outcomes including length of stay and mortality metrics.

Should we implement this into our practice?

Probably. There seems to be no reason to intentionally target a supra-normal PaO₂ in general ICU populations. A large multi-centre randomised controlled trial is needed to establish whether the mortality benefit seen with normoxia in this study is replicable.

References

1. Ridler N, Plumb J, Grocott M. Oxygen Therapy in Critical Illness: Friend or Foe? A Review of Oxygen Therapy in Selected Acute Illnesses. *J Intensive Care Soc* 2014;15(3):190–8.
2. Grocott MPW, Martin DS, Levett DZH, McMorrow R, Windsor J, Montgomery HE. Arterial Blood Gases and Oxygen Content in Climbers on Mount Everest. *N Engl J Med* 2009;360(2):140–9.
3. Kallet RH, Matthay MA. Hyperoxic Acute Lung Injury. *Respir Care* 2013;58(1):123–41.
4. Damiani E, Adrario E, Girardis M, et al. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. *Crit Care* [Internet] 2014 [cited 2016 Nov 30];18(6). Available from: <http://ccforum.biomedcentral.com/articles/10.1186/s13054-014-0711-x>
5. Bassler D, Briel M, Montori VM, et al. Stopping randomised trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *JAMA* 2010;303(12):1180–7.
6. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome. *N Engl J Med* 2010;363(12):1107–16.
7. de Jonge E, Peelen L, Keijzers PJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 2008;12(6):R156.



8. Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA* 2010;303(21):2165–71.
9. Bellomo R, Bailey M, Eastwood GM, et al. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. *Crit Care Lond Engl* 2011;15(2):R90.
10. Eastwood G, Bellomo R, Bailey M, et al. Arterial oxygen tension and mortality in mechanically ventilated patients. *Intensive Care Med* 2012;38(1):91–8.
11. Sutton ADJ, Bailey M, Bellomo R, Eastwood GM, Pilcher DV. The association between early arterial oxygenation in the ICU and mortality following cardiac surgery. *Anaesth Intensive Care* 2014;42(6):730–5.
12. Young P, Beasley R, Bailey M, et al. The association between early arterial oxygenation and mortality in ventilated patients with acute ischaemic stroke. *Crit Care Resusc J Australas Acad Crit Care Med* 2012;14(1):14–9.
13. Stub D, Smith K, Bernard S, et al. Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction. *Circulation* 2015;131(24):2143–50.
14. Suzuki S, Eastwood GM, Glassford NJ, et al. Conservative Oxygen Therapy in Mechanically Ventilated Patients: A Pilot Before-and-After Trial*. *Crit Care Med* 2014;42(6):1414–22.
15. Panwar R, Hardie M, Bellomo R, et al. Conservative versus Liberal Oxygenation Targets for Mechanically Ventilated Patients. A Pilot multi-centre randomised Controlled Trial. *Am J Respir Crit Care Med* 2016;193(1):43–51.
16. Kilgannon JH, Jones AE, Parrillo JE, et al. Relationship Between Supranormal Oxygen Tension and Outcome After Resuscitation From Cardiac Arrest. *Circulation* 2011;123(23):2717–22.
17. Suzuki S, Eastwood GM, Peck L, Glassford NJ, Bellomo R. Current oxygen management in mechanically ventilated patients: a prospective observational cohort study. *J Crit Care* 2013;28(5):647–54.



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Panwar R, Hardie M, Bellomo R, Barrot L, Eastwood G, Young P et al. Conservative versus Liberal Oxygenation Targets for Mechanically Ventilated Patients- A Pilot multi-centre Randomised Controlled Trial. Am J Respir Crit Care Med 2016;193(1):43-51

Introduction

Organ system failures can develop from a myriad of pathological insults, with variable contributions from pre-existing disease and host immune responses. Most intensive care unit (ICU) interventions can be classified as supportive rather than disease-modifying and are applied generically alongside disease-specific therapies. Much recent ICU research has focused on identifying benefit or harm within these realms, studying areas such as mechanical ventilation, fluid administration and renal replacement therapy.¹⁻³ Oxygen therapy is one such area, with prior focus ranging from a pursuit of maximal tissue oxygen delivery to an awareness of the harmful pulmonary effects of high inspired oxygen concentrations in ARDS.⁴

Several large-scale retrospective studies have suggested hyperoxaemia (high PaO₂) may be associated with harm in both specific disease states and generic ICU populations.^{5,6} The Australian and New Zealand Intensive Care Society (ANZICS) trial groups have published large cohort studies of similar patient groups that have challenged these results and not associated hyperoxaemia with harm.⁷⁻¹⁰ The same group has previously delivered landmark pragmatic randomised controlled trials examining aspects of supportive ICU care that have changed international practice.^{2,11,12} In this study the ANZICS group randomised patients between a conservative and liberal oxygenation strategy, designed to be a pilot study to inform a future large-scale trial examining outcomes from these strategies in the critically ill.

Study synopsis

This randomised controlled trial was conducted between 2013 and 2014 in 4 ICUs in Australasia and France. Ethical approval and informed patient / surrogate consent were obtained. Eligible patients were receiving invasive mechanical ventilation (MV) for less than 24 hours and which was expected to continue for at least 24 hours further. Exclusion criteria were lack of clinician equipoise, pregnancy or expected imminent death. Randomisation was computerised and by random block sizes.

The intervention was delivered by the bedside staff titrating the FiO₂ between 0.21 and 0.80 with a target SpO₂ of 88% to 92% in the conservative arm and ≥ 96% in the liberal oxygenation group; continued for the duration of MV unless the FiO₂ was ≥0.6 and the treating physician deemed an altered target necessary. Positive end-expiratory pressure (PEEP) levels were clinician-decided also. Four-hourly data for oxygenation settings and parameters were recorded for 7 days.



As a pilot study there was no formal power calculation and primary endpoints were based on achieving separation between the groups (difference in SpO₂, SaO₂, PaO₂ and FiO₂ by area-under-curve (AUC) analysis over the course of the study). Clinical outcomes such as mortality, length of stay, change in organ-failure scores and ventilator-free days were pre-specified secondary endpoints.

104 out of 357 screened patients were enrolled, with 53 and 51 patients randomised to the conservative and liberal oxygenation groups respectively. Most (120) screened patients were excluded as they had received >24 hours of MV, with 69 excluded as the clinician lacked equipoise. One patient later withdrew consent; the remaining 103 patients were included in the intention-to-treat analysis. Baseline characteristics were similar in the conservative and liberal oxygenation groups: mean age was 62.4 in both; 62% / 65% were male and 75% / 80% medical admissions respectively. Median APACHE III score was non-significantly higher in the conservative group (79.5 vs 70; P=0.06) and baseline mean PaO₂:FiO₂ ratios were similar (248 vs 247 mm Hg).

There was statistically significant (P<0.001) separation in all oxygenation parameters between the groups when measured by AUC analysis over 7 days (primary outcomes). The conservative oxygenation arm had a mean (95% CI) SpO₂ of 93.4% (92.9% to 93.9%); mean FiO₂ of 0.26 (0.25 to 0.28) and mean PaO₂ of 70 mm Hg (68 to 73 mm Hg). The liberal arm had a mean SpO₂ of 97% (96.5 to 97.5%); mean FiO₂ of 0.36 (0.34 to 0.39) and mean PaO₂ of 92 mm Hg (89 - 96 mm Hg). The conservative group spent significantly more time outside the target SpO₂ range (14% vs 3%; P<0.001, mainly above target) and had significantly more oxygen desaturation episodes (SpO₂ <86% for >5 minutes, median 1 per patient vs 0 per patient; P <0.01). The liberal oxygenation group had significantly more SpO₂ and PaO₂ readings in the hyperoxic range: SpO₂ >98% with FiO₂ >0.21 22% vs 4% of readings, P<0.001; PaO₂ >120 mm Hg with FiO₂ >0.21 13% vs 3% of readings; P<0.001.

There were no statistically significant effects of the interventions on the measured clinical secondary outcomes (change in SOFA score or PaO₂:FiO₂ ratio; onset of ARDS; change in creatinine; days free from ventilation, vasopressors or arrhythmias; ICU or 90-day mortality; ICU or hospital length of stay). Median vasopressor dose was significantly less in the liberal oxygenation group (0.04 vs 0.08 µg/kg/min; P=0.009); possibly due to a vasoconstrictor effect of high tissue oxygen levels, duration of vasopressor use did not differ. Fluid balance and ventilatory parameters including PEEP, airway pressures, tidal volumes and minute ventilation also did not differ between the two study arms. No significant effects were seen on the prespecified subgroup analyses of patients with a baseline PaO₂:FiO₂ ratio less than 300 mm Hg or when survivors were compared with non-survivors.



Study critique

This was a successful pilot study, demonstrating consistent application of the chosen protocol resulting in clear statistical separation of the oxygenation parameters between the two groups. Large amounts of detailed longitudinal oxygenation data are presented in the paper and online supplement that would inform the design of a follow-up study. The group was able also to collect and present comprehensive information on clinical outcomes. Despite being multi-centre and international the number of patients recruited was small and the authors correctly emphasise the risk of over-interpreting the clinical outcome data as evidence of the safety (or lack of benefit) of a conservative oxygenation strategy. There are several factors worth considering, especially if comparing the results of this study to the significant outcome benefit from a conservative oxygenation strategy found in the Oxygen-ICU trial also published this year.¹³

This pilot study really compared two controlled oxygenation strategies, with the liberal oxygenation group having a mean FiO_2 of 0.36, giving a mean PaO_2 in the normal range (92 mm Hg, 12.3 kPa) and a $\text{PaO}_2 > 120$ mm Hg (16kPa) on only 13% of time points during the first 7 days. The protocol in this group allowed a reduction in FiO_2 if the SpO_2 was $\geq 96\%$. This is in contrast to the protocol for the Oxygen-ICU study wherein the liberal oxygenation arm received a FiO_2 of at least 0.4 unless the PaO_2 rose above 150 mm Hg (20 kPa); and is also more conservative than that seen in uncontrolled observational studies in this field. The frequency of PaO_2 values above 150mm Hg in the CLOSE study is unfortunately not presented but was presumably uncommon. It is feasible the CLOSE protocol achieved statistical group separation without the magnitude of difference required to show a clinical benefit.

The primary use of SpO_2 , rather than PaO_2 , as a target is consistent with common clinical practice, but SpO_2 varies depending on factors that affect the oxygen-haemoglobin dissociation curve including PaCO_2 and pH as well as PaO_2 , and therefore may not reliably identify hyperoxaemia. PaO_2 is not an ideal alternative to this however as its accuracy depends on the frequency of ABG sampling.

There was considerable overlap in SpO_2 levels between groups, largely due to conservative group patients either having a SpO_2 above target without supplemental oxygen or receiving supplementary oxygen when the trial protocol suggested it was unnecessary. Both of these may have diminished any treatment effect.

The investigators comment on other potential limitations to their study including the lack of blinding and failure to assess delirium rates or ventilatory parameters such as plateau pressure. The latter are worthy of consideration for future study but it is difficult to envision a protocol that can safely blind bedside clinicians to the delivered oxygen concentration. Similarly, the allowance for clinician decision-making with regards



to equipoise when screening patients and if clinical circumstances demanded could be seen as a strength.

As there was no signal of any potential mortality benefit with the intervention the primary aim of a larger trial with the same methodology may be to more firmly establish the safety of the conservative oxygen strategy. The manuscript provides workings explaining that based on subgroup analysis of the CLOSE data an 800 patient study would be adequately powered to detect a 2.6 day difference in ventilator-free days; a much larger study would undoubtedly be required if mortality was the chosen endpoint as any difference is likely to be small.

This highlights the importance of the care given in the non-intervention group to trial design. Previous single-centre critical care studies have had positive results but been criticised due to potential excess mortality in the control group;^{14,15} and the ANZICS trial groups have subsequently delivered pragmatic large multi-centre studies which have established the safety of routine care delivered in high-quality institutions.^{2,11} This allows confidence that potential harm from generic ICU 'therapies' is minimised whilst still allowing for beneficial effects to be looked for in specific patient or disease groups. In this context, it could be argued that the CLOSE liberal oxygenation strategy delivering modest hyperoxia is ethically more appropriate for future study than the (possibly harmful) excess hyperoxia seen in the Oxygen-ICU control arm. Hopefully the planned ANZICS trial group study aiming to recruit 1,000 patients to conservative or standard oxygen therapy (ICU-ROX, CTG 1415-04) may give further insights into this crucial area of ICU care.¹⁶

Where this sits in the body of evidence

Two large retrospective cohort studies suggested a potential harmful association between hyperoxia and ICU outcome.⁶ The ANZICS trials group cohort studies generally refuted these⁷⁻¹⁰ Prospective studies in this area are limited to non-ICU studies,^{17,18} a before-and-after ICU trial¹⁹ and the Oxygen-ICU trial.¹³

In 2008 de Jonge et al reviewed data on 36,307 patients admitted between 1999 and 2006 from the Dutch national intensive care registry.⁵ Regression analysis revealed a 'U' shaped relationship between first-24 hour PaO₂ and in-hospital mortality, which remained after correction for demographics and SAPS II score (PaO₂ ≥16 kPa associated with OR for mortality of 1.23; 95% CI, 1.13 to 1.34). Beyond 24 hours a high FiO₂ (but not PaO₂) was a predictor of mortality independent of selected potential confounders including PaO₂:FiO₂ ratio and SAPS II score.

In 2010 the EMSHockNet investigators published a retrospective cohort study of 6326 post-cardiac arrest patients admitted to 120 US ICUs from 2001-2005.⁶ Overall survival was 44%, 34% with independent functional status. Mortality was significantly higher in



the hyperoxaemia ($\text{PaO}_2 \geq 300$ mm Hg) group than both the 'hypoxia' ($\text{PaO}_2 \leq 60$ mm Hg or $\text{PaO}_2:\text{FiO}_2 \leq 300$) group (63% vs 57%, difference 6% (95% CI 3-9%, $P < 0.001$)); and than the 'normoxaemia' (other PaO_2 values) group (63% vs 45%, difference 18% (95% CI 14-22%, $P < 0.001$)). Oxidative stress following reperfusion was the suggested pathological mechanism. Unfortunately the use of $\text{PaO}_2:\text{FiO}_2$ ratios would categorise patients with impaired oxygen transfer as hypoxic despite a normal or high PaO_2 . In a subsequent publication the same authors described a dose-dependent relationship between the highest PaO_2 in the first 24 hours in ICU and in-hospital mortality (6% increase in mortality per 25 mm Hg increase in PaO_2).²⁰

In contrast Bellomo et al in 2011 applied the same methodology to the ANZICS ICU database and found that when corrected for potential confounders including FiO_2 hyperoxia was not an independent predictor of mortality in 12,108 post non-traumatic cardiac arrest patients.⁷ This group also separately analysed patients with true hypoxia ($\text{PaO}_2 \leq 60$ mm Hg), which was associated with poor outcomes.

In 2012 Eastwood et al retrospectively extracted first-24 hour oxygenation data from the ANZICS database for 152,680 patients admitted to Australian and New Zealand ICUs from 2000 to 2009.⁸ Hyperoxia ($\text{PaO}_2 > 120$ mm Hg (16 kPa)) was present in 49.8%. When adjusted for baseline characteristics and illness severity there was no association between raised PaO_2 and in-hospital mortality.

In 2014 the same methodology was used to examine outcomes following cardiac surgery in 83,060 patients identified from the ANZICS database and admitted between 2003 and 2012.⁹ There was no association between first-24 hour hypoxia and ICU mortality when 'hyperoxic' patients were compared to 'normoxic'; there was a clinically insignificant (0.1 day) difference in ICU and hospital length of stay that was statistically significant.

In 2012 data on 2463 mechanically ventilated patients with ischaemic stroke (identified by APACHE III coding) admitted between 2000 and 2009 was extracted from the ANZICS database.¹⁰ Median PaO_2 was 117 mm Hg (IQR 87 to 196 mm Hg). There was no association between recorded first-24 hour PaO_2 levels and clinical outcomes (mortality, length of stay or discharge home).

In 2015 the AVOID investigators randomised 638 patients with suspected acute myocardial infarction (MI) to 8l/min supplemental oxygen or oxygen only if SpO_2 fell below 94%.¹⁸ The primary analysis was restricted to 441 patients with confirmed ST-elevation MI. There was a significantly raised mean peak creatinine kinase (but not troponin-T) in the supplemental oxygen group (RR 1.26; 95% CI 1.05 to 1.52; $P = 0.01$). The supplemental oxygen group also had significantly more dysrhythmias and re-infarctions within hospital (but not by 6 months) and a larger 6-month infarct size in the 127 patients evaluated for this outcome.



In a 2014 before-and-after feasibility study in a single Australian ICU 54 mechanically ventilated adults treated with a conservative oxygen protocol (target SpO₂ 90% to 92%) were compared with 51 prior patients treated at clinician discretion.¹⁹ Whilst separation was achieved with the conservative group having significantly lower SpO₂, PaO₂ and FiO₂ values on time-weighted analysis there was no difference in the chosen primary outcome of PaO₂:FiO₂ ratios. Exploratory secondary outcomes did not suggest harm. The conventional group had been the subject of a previously published observational cohort study by the same authors.²¹

In 2016 the Oxygen-ICU investigators randomised 480 ICU patients to conservative (PaO₂ 70 to 100 mm Hg, SpO₂ 94 to 98%) or conventional (PaO₂ ≤150 mm Hg or SpO₂ ≥97%) oxygen therapy in a single Italian ICU; 434 were included in a modified intention-to-treat analysis.¹³ ICU mortality was significantly lower in the conservative group (11.6% vs 20.2%; ARR, 0.086; 95% CI, 0.017 to 0.150; P=0.01). The trial was halted early after an earthquake disrupted the hospital infrastructure and recruitment slowed.

Should we change to routinely using conservative oxygen for ventilated patients?

No. This was a pilot study of 2 controlled oxygenation strategies and not powered for clinical outcomes; whilst awaiting further study extremes of oxygenation should probably not be routine targets in the critically ill.

References

1. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1301–8.
2. The ARISE Investigators and the ANZICS Clinical Trials Group. Goal-Directed Resuscitation for Patients with Early Septic Shock. *N Engl J Med* 2014;371(16):1496–506.
3. RENAL Replacement Therapy Study Investigators. Intensity of Continuous Renal Replacement Therapy in Critically Ill Patients. *N Engl J Med* 2009;361(17):1627–38.
4. Ridler N, Plumb J, Grocott M. Oxygen Therapy in Critical Illness: Friend or Foe? A Review of Oxygen Therapy in Selected Acute Illnesses. *J Intensive Care Soc* 2014;15(3):190–8.
5. de Jonge E, Peelen L, Keijzers PJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 2008;12(6):R156.
6. Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA*



2010;303(21):2165–71.

7. Bellomo R, Bailey M, Eastwood GM, et al. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. *Crit Care Lond Engl* 2011;15(2):R90.
8. Eastwood G, Bellomo R, Bailey M, et al. Arterial oxygen tension and mortality in mechanically ventilated patients. *Intensive Care Med* 2012;38(1):91–8.
9. Sutton ADJ, Bailey M, Bellomo R, Eastwood GM, Pilcher DV. The association between early arterial oxygenation in the ICU and mortality following cardiac surgery. *Anaesth Intensive Care* 2014;42(6):730–5.
10. Young P, Beasley R, Bailey M, et al. The association between early arterial oxygenation and mortality in ventilated patients with acute ischaemic stroke. *Crit Care Resusc J Australas Acad Crit Care Med* 2012;14(1):14–9.
11. The NICE-SUGAR investigators. Intensive versus Conventional Glucose Control in Critically Ill Patients. *N Engl J Med* 2009;360(13):1283–97.
12. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. *N Engl J Med* 2012;367(20):1901–11.
13. Girardis M, Busani S, Damiani E, et al. Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU randomised Clinical Trial. *JAMA* 2016;316(15):1583.
14. Van den Berghe G, Wouters P, Weekers F, et al. Intensive Insulin Therapy in Critically Ill Patients. *N Engl J Med* 2001;345(19):1359–67.
15. Rivers E, Nguyen B, Havstad S, et al. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. *N Engl J Med* 2001;345(19):1368–77.
16. Young, Paul. CTG-Research - ICU-ROX [Internet]. [cited 2016 Dec 17]; Available from: <http://www.anzics.com.au/Lists/CTGResearch/DispForm.aspx?ID=94&Source=http%3A%2F%2Fwww%2Eanzics%2Ecom%2Eau%2Fpages%2FCTG%2Fcurrent%2Dresearch%2Easpx&ContentTypeld=0x01002FB135486A37EB43A4F22792A9913B8A>
17. Meyhoff CS, Wetterslev J, Jorgensen LN, et al. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: the PROXI randomised clinical trial. *JAMA* 2009;302(14):1543–50.
18. Stub D, Smith K, Bernard S, et al. Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction. *Circulation* 2015;131(24):2143–50.
19. Suzuki S, Eastwood GM, Glassford NJ, et al. Conservative Oxygen Therapy in Mechanically Ventilated Patients: A Pilot Before-and-After Trial*. *Crit Care Med* 2014;42(6):1414–22.
20. Kilgannon JH, Jones AE, Parrillo JE, et al. Relationship Between Supranormal



Oxygen Tension and Outcome After Resuscitation From Cardiac Arrest. *Circulation* 2011;123(23):2717–22.

21. Suzuki S, Eastwood GM, Peck L, Glassford NJ, Bellomo R. Current oxygen management in mechanically ventilated patients: a prospective observational cohort study. *J Crit Care* 2013;28(5):647–54.

DIABOLO

Faisy C, Meziani F, Planquette B, Clavel M, Gacouin A, Bornstain C, et al. Effect of Acetazolamide vs Placebo on Duration of Invasive Mechanical Ventilation Among Patients With Chronic Obstructive Pulmonary Disease. A Randomised Clinical Trial. JAMA 2016;315(5):480-488

Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by irreversible airflow limitation and caused by both small airway disease and destruction of lung parenchyma.¹ Exacerbation of COPD is a frequent cause of ICU admission. Patients with this condition often present a challenge in weaning from mechanical ventilation and can have a hospital mortality of up to 24%. For those admitted to ICU over the age of 60, mortality can increase from 30% at hospital discharge to 59% at 1 year.²

Respiratory acidosis and metabolic alkalosis are the most common acid-base disturbances seen in mechanically ventilated COPD patients. Aside from occurring secondary to hypercapnoea, metabolic alkalosis can also occur develop for other reasons, such as steroid use, diuretic use, hypokalaemia and hypophosphataemia.³ The presence of metabolic alkalosis has also been associated with increased morbidity and mortality.⁴ The carbonic anhydrase inhibitor, acetazolamide, has been used for decades as a respiratory stimulant in patients with COPD and metabolic alkalosis.⁵ The reduction in pH associated with the use of acetazolamide in metabolic alkalosis is thought to be mediated via a reduction in the serum strong ion difference through increased tubular sodium excretion and chloride retention.⁶

Although the biochemical effects of acetazolamide are well known, whether these translate into clinically relevant outcomes is much less clear. Evidence for the use of acetazolamide in mechanically ventilated COPD patients is confined to two small retrospective case-control studies.^{6,7} No previous randomised controlled trials have been published regarding whether or not acetazolamide reduces the duration of mechanical ventilation in COPD patients requiring invasive mechanical ventilation. As such this trial is an important addition to the literature.

Study synopsis

DIABOLO was a multi-centre randomised, double-blind, placebo-controlled trial undertaken in 15 intensive care units in France. The investigators hypothesized that acetazolamide, in doses of $\geq 1,000$ mg/day, would shorten the duration of mechanical ventilation in critically ill patients with COPD.

Patients with a history of COPD were eligible for enrolment if they were admitted to ICU



and required invasive mechanical ventilation. Within 24 hours of initiation of invasive ventilation patients were randomised to receive either 500mg or 1,000 mg (when loop diuretics were co-prescribed) of acetazolamide twice daily or placebo (10ml of saline), for a maximum of 28 days. Randomised patients only received study drug if they developed either a pure or a mixed metabolic alkalosis. Metabolic alkalosis was defined as serum bicarbonate of more than 26mEq/L and arterial pH of 7.35 or more.

Randomisation was via computer-generated assignment sequence in a centralized, blinded fashion. Stratification by centre and for baseline respiratory status of the patient occurred. The primary end-point was the duration of invasive ventilation. When calculating the sample size the authors used data from previous preliminary work. 380 patients were required to identify a 15% relative reduction in duration of mechanical ventilation, from a median (IQR) of 12 (5) days to be enrolled to achieve 80% power at a 2-sided α level of 0.05. Analyses were performed on the intention-to-treat population and then confirmed on the per-protocol population (defined as the set of patients who did not perform any protocol violation that may interfere with primary criteria evaluation).

694 patients were assessed for eligibility. 382 were randomised – 188 to receive acetazolamide and 194 to the placebo group. One patient in each group was incorrectly included in randomisation leaving an intention-to-treat population of 380 patients. 28.3% (n=53) of patients in the acetazolamide group and 22.2% (n=43) of patients in the placebo group did not receive the intervention as randomised, because these patients either did not develop a metabolic alkalosis or had a temporary contraindication.

The two groups were well matched at baseline for age, sex and severity of illness (SAPS II and SOFA) scores. Groups were balanced in terms of respiratory status before hospitalization (26% of patients in each group were on home oxygen therapy). Use of glucocorticoids and loop diuretics prior to hospitalisation was also well matched between groups. Laboratory measurements at inclusion showed that serum protein, creatinine and potassium levels were similar in both groups. The mean pH and serum bicarbonate (mEq/L), at enrolment did not differ between groups, 7.32 (0.11) vs 7.30 (0.12) and 26.9 (6.9) vs 27.4 (6.6) respectively. The mean PaCO₂ (mm Hg) was 52.5 (16) vs 55.6 (17) in the acetazolamide vs placebo groups, respectively.

The most common reason for invasive ventilation in both treatment groups was community-acquired pneumonia, at 44.3% and 43%. More patients in the acetazolamide group had left ventricular insufficiency as a cause for invasive ventilation 43 (23%) vs 32 (16.6%). Other diagnoses accounted for 27.8% and 22.8% of the reasons for invasive ventilation in the treatment and control groups, respectively.

Readiness to wean was defined according to the criteria of the Sixth International



Consensus Conference on Intensive Care Medicine (2005).⁷ Weaning was tailored by the treating clinician but involved reductions in pressure support or volume assisted ventilation with progressively longer times on a T-piece. Criteria for extubation and re-intubation were standardized. Prophylactic use of non-invasive ventilation was permitted. If patients did not require the reintroduction of invasive ventilation within 48 hours of extubation, the weaning was defined as a success.

The total durations of invasive ventilation were (median/IQR) 136.5 hours (68.7 to 234.7) in the acetazolamide group vs 163 (86.2 to 242.9) in the placebo group. The between-group difference of -16.0 hours (95% CI, -36.5 to 4) did not reach statistical significance. Secondary outcomes, such as duration of weaning off invasive ventilation, numbers of spontaneous breathing trials, use of tracheostomy or non-invasive ventilation after extubation, length of ICU stay and ICU mortality rate did not differ significantly between groups.

Acetazolamide achieved significantly larger decreases in the median daily serum bicarbonate (-0.3 mEq/L; IQR, -1 to 0.4 mEq/L vs 0.3 mEq/L; IQR, -0.2 to 1.3 mEq/L). Median daily PaO₂:FiO₂ (7.8 mm Hg; IQR, -1.5 to 20.5 mm Hg vs 3.5 mm Hg; IQR, -5.2 to 13.9 mm Hg) was significantly greater in the acetazolamide group compared with placebo. The number of days with metabolic alkalosis and treatment doses were also significantly lower in the acetazolamide group, 2 vs 4 days and 2 vs 6 days, respectively. No significant differences were identified in any post hoc subgroup analysis.

Study critique

Although the theoretical basis for this trial was sound and clear definitions were used throughout, in attempting to explain the lack of beneficial effect of acetazolamide on duration of mechanical ventilation seen in this trial, the study population requires particular discussion.

The patients in this trial were a heterogenous group of predominantly medical patients with COPD. A significant proportion had left ventricular insufficiency as a cause for invasive ventilation and many had either unknown or other causes - 33.1% vs 27.5% in the treatment and control groups, respectively. This was therefore not a study population of patients admitted with a severe exacerbation of COPD, rather a study of patients admitted to ICU who also had COPD. A more homogenous COPD study population, with exacerbation of COPD as the primary reason for intubation, may arguably have led to differing results.

The mean pH in both groups at baseline indicated an acidaemia as the predominant metabolic process which was present rather than an alkalaemia. Baseline serum potassium, protein and renal function was similar between groups. Cumulative fluid balance of the groups was not measured. Only 59 out of 187 (31.5%) patients had a pure



metabolic alkalosis at baseline in the acetazolamide group compared to 50 out of 193 (26%) in the placebo group. The majority of patients in this trial had at best, a mild mixed metabolic alkalosis. Again this begs the question of whether the correct patient group from a metabolic point of view, was targeted in this study.

Patients were randomised within 24 hours of invasive ventilation and test treatment was administered from day 1 in those with metabolic alkalosis. The degree of metabolic alkalosis in this patient group may have been too mild and perhaps treatment started too early to elucidate any statistically significant difference between groups. 53 out of 187 (28%) patients in the acetazolamide group and 43 out of 194 (22%) patients in the placebo group never received any intervention as although they met inclusion criteria for the study (COPD and mechanical ventilation) they failed to develop the necessary metabolic alkalosis to receive the study drug. This highlights the relatively benign eligibility criteria for inclusion in the trial and lends further credence to the argument that the phenotype of this study population prevented the study question from being answered.

Post hoc subgroup analyses included those patients ventilated for longer than 96 hours and those with a pure metabolic alkalosis at baseline. In neither of these patient groups was the duration of weaning or invasive ventilation shorter in the acetazolamide group compared to placebo. Acetazolamide had no significant impact on minute ventilation in this trial. A higher dose of acetazolamide was used in this study compared to previous uncontrolled studies but the mean change in serum bicarbonate in the treatment group was very low (-0.3mEq/L) and the mean change in pH in the acetazolamide group was 0. These laboratory findings suggest perhaps that the dose used was inadequate to create the biochemical conditions necessary to stimulate the respiratory centres and hence reduce the duration of mechanical ventilation.

In planning the trial, the investigators estimated a median duration of invasive ventilation in the placebo group of 12 days. The trial was prospectively powered to detect a 15% difference in invasive ventilation duration. The observed median duration of invasive ventilation in both groups was lower than anticipated for statistical power. The clinically important reduction in duration of invasive ventilation in the acetazolamide group may therefore not have reached statistical significance due to lack of power.

Where this sits in the body of evidence

In a single-centred, retrospective case-control study, with 1:1 matching, patients were identified and defined as cases if they had received 500mg acetazolamide and considered as controls if they had not. 36 patients in each group were matched according to age, SAPSII score, arterial pH and PaO₂:FiO₂ on admission. Patients who had received acetazolamide were found to have significantly reduced serum bicarbonate, PaCO₂ and pH compared with controls. There were no differences detected for ICU



length of stay or ICU mortality although the study lacked the necessary power to detect differences in clinical outcome measures.⁸

In another single-centred case-control study, 26 intubated COPD patients with a mixed metabolic alkalosis received a single daily dose of 500mg of acetazolamide. This group was compared with a historical control group who were matched for age, severity of illness, serum bicarbonate and arterial pH. Although acetazolamide reduced serum bicarbonate there was no effect on PaCO₂ or respiratory parameters in weaning COPD patients from invasive ventilation.⁹

In a single-centred randomised, double-blind trial, 40 mechanically ventilated patients, with COPD or asthma, who also had a metabolic alkalosis (arterial pH > 7.48 and serum bicarbonate ≥ 26 mEq/L), were randomised to receive either a single intravenous dose of 500mg of acetazolamide or 250mg 6-hourly for a total of 4 doses. Data was collected for serum bicarbonate, serum potassium, arterial pH, urine chloride and pH for the following 72 hours. Both dosing regimens were found to significantly reduce the serum bicarbonate concentration. No significant differences were found at any point during the study between the two dosing regimens for serum bicarbonate, serum potassium or urine chloride end points. There was no difference between diuretic and non-diuretic treated patients. No clinically relevant end point was assessed in this study.¹⁰

The optimal dosage of acetazolamide in ICU patients is not known. In a single-centre retrospective observational study Heming et al, used pharmacodynamic modelling and simulation, to assess the effect of different acetazolamide doses on physiological respiratory parameters (mode of mechanical ventilation, respiratory rate, tidal volume and minute ventilation). Only slightly increased minute ventilation without decreased PaCO₂ levels were seen in response to doses of 250mg-500mg twice daily. Simulations indicated that doses of >1,000mg/day would be needed to significantly increase minute ventilation. Pharmacodynamic modelling and simulation suggests the mechanism of this increase would be via an increase in respiratory rate rather than tidal volume.¹¹

The TRAMA Trial (NCT01499485) is another phase III double-blind, multi-centre, randomised controlled trial involving Spanish ICUs. This trial will analyse whether treatment with acetazolamide, of intubated patients suffering from COPD or obesity hypoventilation syndrome, reduces the duration of mechanical ventilation. Eligible patients were randomised to receive either 500mg of acetazolamide or placebo. It has completed recruitment and data collection.¹²

Should we implement this into our practice?

No. This trial does not support the use of acetazolamide to reduce the duration of mechanical ventilation in invasively ventilated COPD patients with mild mixed metabolic alkalosis.



References

1. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176(6):532–555.
2. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. *JAMA* 1995;274(23):1852–1857.
3. Webster NR, Kulkarni V. Metabolic Alkalosis in the Critically Ill. *Crit Rev Clin Lab Sci* 1999;36(5):497–510.
4. Hodgkun JE, Soepronno FF, Chan DM. Incidence of metabolic alkalemia in hospitalized patients. *Crit Care Med* 1980;8(12):725–728.
5. Swenson ER. Carbonic anhydrase inhibitors and ventilation: a complex interplay of stimulation and suppression. *Eur Respir J* 1998;12(6):1242–1247.
6. Moviat M, Pickkers P, van der Voort PH, van der Hoeven JG. Acetazolamide-mediated decrease in strong ion difference accounts for the correction of metabolic alkalosis in critically ill patients. *Crit Care* 2006;10(1):1.
7. Boles J-M, Bion J, Connors A, et al. Weaning from mechanical ventilation. *Eur Respir J* 2007;29(5):1033–1056.
8. Bahloul M, Chaari A, Tounsi A, et al. Impact of acetazolamide use in severe exacerbation of chronic obstructive pulmonary disease requiring invasive mechanical ventilation. *Int J Crit Illn Inj Sci* 2015;5(1):3.
9. Faisy C, Mokline A, Sanchez O, Tadié J-M, Fagon J-Y. Effectiveness of acetazolamide for reversal of metabolic alkalosis in weaning COPD patients from mechanical ventilation. *Intensive Care Med* 2010;36(5):859–863.
10. Mazur JE, Devlin JW, Peters MJ, Jankowski MA, Iannuzzi MC, Zarowitz BJ. Single versus multiple doses of acetazolamide for metabolic alkalosis in critically ill medical patients: a randomised, double-blind trial. *Crit Care Med* 1999;27(7):1257–1261.
11. Heming N, Faisy C, Urien S. Population pharmacodynamic model of bicarbonate response to acetazolamide in mechanically ventilated chronic obstructive pulmonary disease patients. *Crit Care* 2011;15(5):1.
12. Heming N, Urien S, Faisy C. Acetazolamide: a second wind for a respiratory stimulant in the intensive care unit? *Crit Care* 2012;16(4):1.



Rehabilitation in Acute Respiratory Failure

Morris PE, Berry MJ, Files DC, Thompson JC, Hauser J, Floreset L et al. Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure A randomised Clinical Trial. JAMA 2016; 315(24):2694-2702

Introduction

Survival after critical illness is associated with physical disability, reduced quality of life and psychological problems.¹ This multi-faceted spectrum of sequelae following critical illness has been termed 'post intensive care syndrome'.² Patients suffer from extreme fatigue and muscle weakness which may delay rehabilitation.³ Skeletal muscle wasting is a common complication and is associated with the severity of illness and duration of mechanical ventilation.^{4,5} Rehabilitation is a key strategy in the recovery of patients after critical illness. However, despite improved awareness, our understanding of the pathophysiology of post intensive care syndrome remains limited.⁶ Hence, the optimum treatment strategy remains elusive. Early interventions (in the intensive care) aimed at the prevention of muscle atrophy may improve outcome.^{7,8} However early rehabilitation may not always be practical or even possible. Furthermore, the efficacy of intervention in the intensive care is not entirely established.⁹ Post intensive care rehabilitation trials when physiotherapy may be more easily delivered however, have not been able to conclusively demonstrate improved outcomes.⁵ Rehabilitation after intensive care discharge may be too late or perhaps the most efficacious intervention has not been investigated. Current evidence for the timing, duration and method of rehabilitation is limited. Despite the paucity of evidence, guidelines recommend post critical illness rehabilitation.¹⁰ Therefore further research in this important aspect of care is urgently required.

Study synopsis

This was a single-centre, assessor blinded randomised trial in a medical intensive care unit in America. The aim was to investigate the effect of a standardised rehabilitation program on hospital length of stay after critical care admission for acute respiratory failure.

All adult patients admitted to the medical intensive with a PaO₂/FiO₂ ratio less than 300 mm Hg who required ventilatory support were screened for enrolment. Patients were excluded if they were immobile or had cognitive impairment prior to admission, had a body mass index >50 kg/m², had a condition limiting rehabilitation such as neuromuscular disease, spinal pathology, acute stroke or hip fracture or had been mechanically ventilated for more than 80 hours or hospital admission greater than seven



days.

Patients were randomised using a computer generated sequence to either standardised rehabilitation therapy (SRT) or standard care. The SRT comprised three exercise types: passive motion, physical therapy and progressive resistance exercises. Passive motion included five repetitions of manipulation of the joints of the arms and legs. Physical therapy included a range of activity including transfers out of bed and to chair, various sitting and standing balance activities and mobilisation. While resistance exercises incorporated elastic resistance bands to exercise upper and lower limbs with the aim of improving functional tasks and activities of daily living. The program was delivered by a rehabilitation team three times per day while the patient was in hospital. Unconscious patients received passive motion while co operative patients progressed to physical therapy and resistance exercises. The usual care group could have physical therapy at the discretion of the treating physicians.

The primary outcome was hospital length of stay. The research team was not involved in discharge decisions or planning. Secondary outcomes included measures of physical function and health related quality of life. Physical function was measured using several indicators: the Short Performance Physical Battery (SPPB) and muscular strength using a handgrip and handheld dynamometer. The SPPB derives a score based on a timed four metre walk, timed performance of five repetitions of a chair to stand test and a standing balance test. Self reported test consisted of the Functional Performance Inventory¹¹ and the physical functioning scale of the 36- Item Short Form Health Survey (SF-36 PFS).¹²

Physical measures were obtained at intensive care and hospital discharge and subsequently at 2,4 and 6 months after enrolment. Health related quality of life was measured using the SF-36 physical health survey and the mental health survey (SF-36 MHS) component summary scores and Mini-Mental State Examination (MMSE) score. These were measured at the same time as the physical measurements but only after discharge. The investigators also recorded days alive, ventilator-free days and days free from intensive care and hospital up to 28 days.

Over a five year period, 4,804 with respiratory failure were screened, 4,186 were excluded. The main exclusions were prior immobility (24%), no lung injury (20%), prolonged admission or ventilation (31%) or moribund state (18%). Of the 618 eligible patients, 300 were randomised, 84 in the SRT and 81 in the usual care group completed follow up at six months. Baseline characteristics were similar. Patients were around 56 years of age, 55% were women, with three quarters of white ethnicity. At randomisation, the mean PaO₂/FiO₂ ratio was 178.6 mm Hg (SD 83.8) and mean CO₂ was 44.1 mm Hg (17.2), with almost one in four patients in shock. There was a significant percentage of patients with chronic lung disease (31%) and perhaps surprisingly almost 20% of patients had home oxygen.



In terms of the intervention, the SRT group received passive motion within a median of 1 day (IQR 0-2), physical therapy within a median of 3 days (1-6) and resistive exercise within a median of 4 days (2-7). While the usual care group received physical therapy within a median of 7 days (4-10). SRT patients had passive motion on 87.1%, physical therapy on 54.6% and resistance exercise on 35.7% of study days compared to 11.7% of study days for physical therapy in the usual care group. For the SRT group, the median days of delivery of therapy per participant was 8 (5- 14) for passive range of motion, 5 (3- 8) for physical therapy, and 3 (1-5) for progressive resistance exercise. The usual care group had a median delivery of 1 day (0-8).

Overall there was no difference in the median hospital length of stay, 10 days (6-17) for the SRT group and 10 days (7-16) for the usual care group (median difference, 0 [95% CI, -1.5 to 3], $P = 0.41$). There was also no difference in length of intensive care stay, days requiring vasopressors, ventilation or sedative drugs, CAM ICU positive days, requirement for restraints used or fluid balance. There were no differences in discharge destination.

In terms of secondary outcomes, there was no difference in the performance based or self reported physical function at ICU or hospital discharge. At hospital discharge 71% of the SRT group and 61% of the usual care could perform a four metre walk ($p=0.15$). There was no difference in the SPPB, SF-36 PFS and FPI scores at 2 or 4 months. However at 6 months these outcomes were significantly better in the SRT group, SPPB difference 1.1 (0.04-2.1) $p=0.04$, SF 36 PFS difference 12.2 (3.8-20.7) $p=0.001$ and FPI difference 0.2 (0.04-0.4) $p=0.02$. At six months 96% of SRT could perform the 4 metre walk versus 88% in the usual care ($p=0.04$). When re-analysed assuming dropouts followed the control group the only remaining significant difference was for the SF36 PFS. Hand strength and dynamometer did not differ at any stage. In terms of health related quality of life there was no difference at any time points.

Post discharge almost half of patients in each group received physiotherapy. At six months 48.7% of the SRT group and 44.7% of the usual care group ($P=0.63$) were alive and hospital admission free.

Study critique

As critical incidence and survival increase, the problems associated with critical illness recovery have become more relevant. Loss of independence after hospital admission is common and perhaps this functional decline is intensifying the bed crisis reported in many hospitals, hence interventions to prevent decline or expedite recovery are critically important.¹³ However, in the early phase of critical care patients are often sedated and clinical focus is on the restoration and correction of life threatening pathophysiology. Attention to rehabilitation has perhaps only been addressed in the recovery phase in intensive care or deferred until ready for ward discharge.⁸ Yet early rehabilitation in the



intensive care unit has been shown to be practicable and safe.¹⁴ Furthermore earlier interventions have shown potential beneficial effects on short term outcome measures.^{8,15} However, the longer term effects of early interventions have not been established.⁹ This trial incorporated the elements of a previously successful early rehabilitation regime¹⁵, added a further resistance element and followed the patients for a longer period of time.

This was a large trial which enrolled 300 patients in total, but the study highlights some of the major problems of conducting rehabilitation research in critical illness. Firstly only 165 patients completed the study. This was due to a combination of deaths (66 patients), withdrawals (15 patients) and participants lost to follow up (54 patients). When 45% of patients do not complete the trial, it is perhaps difficult to draw firm conclusions from the results. The power calculation attempted to compensate for both mortality and dropouts however the rates encountered were higher than expected. The authors conceded that perhaps a mechanism to engage with patients in the outpatient setting might be required, such as ongoing therapy. Although another trial which continued rehabilitation for 8 weeks after discharge had almost identical completion rates, indicating that perhaps such loss of patients is unavoidable.⁹ Statistical analysis may somewhat compensate for dropouts, however rehabilitation and exercise in health requires motivation, perhaps patients who complete these trials are somewhat self selected. Therefore any treatment effect could be masked by the determination of the participants to rehabilitate and perform well on the physical testing. While perhaps the population who fail to complete the trial may have benefited, but they may also require further help and support and that poor health is the reason for non completion.

Another consideration, when conducting rehabilitation research is the time required to complete such studies. This trial was a monumental undertaking requiring over 5 years to completion. After screening over 4,800 patients, only every other eligible patient was recruited. This again has been recognised as an issue, as obtaining consent regarding rehabilitation is difficult from next of kin who at the time are preoccupied with survival rather than exercise regimes.⁹ The failure to be able to randomise patients may not have affected the outcome in this trial, however the length of time required may have. Therapies and standards of care change over time, it is conceivable that the usual care treatment may have been influenced or that other interventions, such as changes in sedation regimes or ventilation practice could affect the severity of functional disability.

Finally, the optimal method of functional assessment of patients after critical illness is not known. Over 250 assessments to measure health related quality of life, physical function, cognition, and mental health outcomes have been used.¹⁶ Therefore comparison of functional status across trials is difficult. The measures used in this trial were multiple, and included both measured and self reported assessments. The short physical performance battery score is a test primarily of lower limb function. The test

was developed as a predictor of disability in an elderly population in an outpatient setting.¹⁷ It has limited validation in the acute setting but has been shown to be responsive to changes following an exercise-based intervention.¹⁷ The patient reported measures were the Functional Performance Inventory (FPI) which is a questionnaire designed to evaluate functional performance in patients with chronic obstructive pulmonary disease and the 36 item short form survey which was developed as part of the Medical Outcomes Study (MOS), a multi-year, multi-site study to explain variations in patient outcomes in the United States. Neither measure has been specifically validated for use in the intensive care population.

Accepting that there are difficulties with rehabilitation studies, this was an interesting trial using multiple physical interventions in an attempt to improve patient function and there are many positive aspects which enhances our current understanding but also poses further questions. The enrolment in this study was different to several other rehabilitation trials which have focused on prolonged ventilation (variably defined from 72 to 120 hours) in the inclusion criteria, on the basis that these patients are potentially the most functionally impaired.^{8,9,18} In this trial patients were recruited on the basis of acute respiratory failure, this crucially allowed the intervention to commence on a median of day one, a truly early intervention, targeting patients when muscle atrophy is just commencing and perhaps early enough to prevent rather than rehabilitate when dysfunction has already occurred. This is an important difference between this trial and two other recent trials which failed to show a difference in outcome at six months.^{9,18} Arguably, this early approach may have recruited patients who would not have progressed to the levels of dysfunction recorded after prolonged ventilation. However, the majority of patients were ventilated, and for a median of four days, and therefore would have met inclusion criteria for most rehabilitation trials. The SPPB at intensive care discharge also confirmed that these patients had significant physical impairment. This impairment occurred despite the early timing of the intervention.

The intervention itself was cleverly planned with initial passive movement when the patient was unable to co operate and progressive increase in muscle loading as the patient was able to participate. The trial showed a clear difference in both the timing and duration of therapy, although a critic might suggest that the usual care had relatively little physiotherapy that may not reflect usual care in some units.^{9,18} The apparent failure to prevent disability or improve strength measures at intensive care discharge may reflect a problem with the frequency, intensity, or duration of physiotherapy. Excessive muscle work has been described with subsequent overuse weakness.¹⁹ Alternatively perhaps the measures used at intensive care discharge are inappropriate, similar disability has been reported in another early rehabilitation trial where there also seemed to be a delayed separation between the groups in favour of the intervention.⁸ Perhaps the early intervention works at an unmeasured level and subsequently allows more accelerated improvement in function. Accelerated recovery



has been postulated recently in another rehabilitation trial.⁹

Ultimately this trial failed to show a benefit of early rehabilitation on length of stay in intensive care or in hospital which is perhaps not surprising given the short length of hospital stay (median 10 days). A previous trial did show benefit of an early intervention in terms of hospital and intensive care stay.¹⁵ The trial used a similar early intervention however the population was sicker with higher hospital mortality and generally longer hospital admissions. Multiple studies^{8,9,20} have shown severe disability at intensive care discharge, with significant improvement prior to hospital discharge and perhaps these longer admissions allowed enough time for the patients in the intervention group to improve sufficiently to be discharged earlier. A slight problem with using hospital discharge as a surrogate of function is that patients are often discharged with disability and discharge locations vary.²⁰

In this current trial improvement in the intervention group was not shown until 6 months post intervention. This is a considerably longer period of time than the separation found in another of early intervention which occurred around two weeks,⁸ to suggest that an intervention which lasted only 8 days might have a lag time of six months is perhaps difficult to explain. Two recent trials failed to show a benefit of intensive physiotherapy on outcomes at six months.^{9,20} The intervention was delivered later perhaps too late in these trials. A further difference was that both groups of patients in these trials had more physiotherapy than the control group in the current trial. Perhaps this diluted any beneficial effect and perhaps a minimum amount of rehabilitation is all that is required to improve outcomes. It is interesting to note that these trials had discharge to home rates around 50% while it was over 80% in the current trial. It may be that the heterogeneity of the populations, interventions, measuring tools and follow up are just too different to compare current trials. Further work is required to identify those patients who develop the most disability and therefore have most to gain. Furthermore the timing, dose and specifics of the ideal intervention is still not known.

Where this sits in the body of evidence

In a prospective cohort study 330 patients ventilated less than 48 hours were assigned to early mobilisation with physiotherapy (n=165) versus usual care (n=165). More Protocol patients received at least one physical therapy session than did Usual Care (80% vs 47%; $P > 0.001$). Protocol patients were out of bed earlier (5 vs 11 days; $P < 0.001$), and had therapy initiated more frequently in the intensive care unit (91% vs 13%; $P < 0.001$). For protocol patients, intensive care unit length of stay was 5.5 vs 6.9 days for Usual Care ($P = 0.025$); hospital length of stay for protocol patients was 11.2 vs 14.5 days for Usual Care ($P = 0.006$).¹⁵

In a two centre randomised control trial 104 adult patients who were ventilated for less than 72 hours were randomised to early exercise and mobilisation (physical and



occupational therapy) during periods of daily interruption of sedation (intervention; n=49) or to daily interruption of sedation with therapy as ordered by the primary care team (control; n=55). Return to independent functional status at hospital discharge occurred in 29 (59%) patients in the intervention group compared with 19 (35%) patients in the control group (OR, 2.7; 95% CI, 1.2 to -6.1; P=0.02). Patients in the intervention group had shorter duration of delirium (median, 2.0 days vs 4.0 days; P=0.02), and more ventilator-free days (23.5 days vs 21.1 days, 95% CI, 0.0 to 23.8; P=0.05) during the 28-day follow-up period than did controls.⁸

In a single-centre, assessor-blinded, randomised controlled trial. 150 participants were stratified and randomised to receive usual care or intervention if they were in the ICU for 5 days or more. The intervention group received intensive exercises in the ICU, ward and outpatients for 8 weeks. Physical function was evaluated using the Six-Minute Walk Test (6MWT) (primary outcome), the Timed Up and Go Test and the Physical Function in ICU Test. Patient-reported outcomes were measured using the Short Form 36 Health Survey, version 2 (SF-36v2) and Assessment of Quality of Life (AQoL) Instrument. No significant differences were found for the primary outcome of 6MWT or any other outcomes at 12 months after ICU discharge.⁹

In a multi-centre randomised trial in America. 120 patients were randomised to intensive physiotherapy group or control. The intensive group received 12.4 ± 6.5 sessions for a total of 408 ± 261 minutes compared with only 6.1 ± 3.8 sessions for 86 ± 63 minutes in the standard-of-care group ($P < 0.001$ for both analyses). Physical function assessments were available for 86% of patients at 1 month, for 76% at 3 months, and for 60% at 6 months. In both groups, physical function was reduced yet significantly improved over time between 1, 3, and 6 months. When we compared the two interventions, there was no differences in the total CS-PFP-10 scores at all three time points ($P = 0.73, 0.29,$ and $0.43,$ respectively) or in the total CS-PFP-10 score trajectory ($P = 0.71$).¹⁸

Should we implement this into our practice?

Possibly not. With no signal of benefit with early mobilisation in this trial, and previous studies reporting mixed results, the place for early mobilisation is now less clear.

References

1. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010; 304(16):1787-94.
2. Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Critical Care Medicine* 2012; 40(2):502-9
3. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F et al; Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *NEJM* 2003; 348(8): 683-693.
4. Puthuchery ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P et al. Acute Skeletal Muscle wasting in critical illness. *JAMA* 2013; 310 (15): 1591-1600.
5. Connolly B, Salisbury L, O'Neill B, Geneen L, Douiri A, Grocott MP et al. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness. *Cochrane Database Syst Rev.* 2015; (6):CD008632.
6. Goddard SL & Adhikari NK. The Challenging Task of Improving the Recovery of ICU Survivors. *JAMA* 2016; 315(24): 2671-2672.
7. Patel BK, Pohlman AS, Hall JB, Kress JP. Impact of early mobilization on glycemic control and ICU-acquired weakness in critically ill patients who are mechanically ventilated. *Chest* 2014; 146 (3): 583-589.
8. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009; 373 (9678):1874-1882.
9. Denehy L, Skinner EH, Edbrooke L, Haines K, Warrillow S, Hawthorne G et al. Exercise rehabilitation for patients with critical illness: a randomised controlled trial with 12 months of follow-up. *Crit Care.* 2013; 17(4):R156.
10. National Institute for Health and Care Excellence. Rehabilitation after critical illness. <http://www.nice.org.uk/guidance/CG83>. Published March 2009.
11. Leidy NK, Hamilton A, Becker K. Assessing patient report of function: content validity of the Functional Performance Inventory-Short Form (FPI-SF) in patients with chronic obstructive pulmonary disease (COPD). *Int J Chron Obstruct Pulmon Dis.* 2012; 7:543-554.
12. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. *Ann Med.* 2001; 33(5):350-357.
13. Sager MA, Franke T, Inouye SK, Landefeld CS, Morgan TM, Rudberg MA et al. Functional outcomes of acute medical illness and hospitalization in older persons. *Arch Intern Med* 1996; 156: 645-52.
14. Bailey P, Thomsen GE, Spuhler VJ, Blair R, Jewkes J, Bezdjian L et al. Early activity is



- feasible and safe in respiratory failure patients. *Crit Care Med* 2007; 35: 139-45.
15. Morris PE, MD; Goad A, RN; Thompson C, Taylor K, Harry B, Passmore L et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med* 2008; 36: 2238-43.
 16. Turnbull AE, Rabiee A, Davis WE, Nasser MF, Venna VR, Lolitha R, et al. Outcome Measurement in ICU Survivorship Research From 1970 to 2013: A Scoping Review of 425 Publications. *Critical Care Medicine* 2016; 44 (7): 1267-77.
 17. Puthoff ML. Outcome Measures in Cardiopulmonary Physical Therapy: Short Physical Performance Battery. *Cardiopulmonary Physical Therapy Journal*. 2008; 19(1):17-22.
 18. Moss M, Nordon-Craft A, Malone D, Van Pelt D, Frankel SK, Laird Warner M et al. A randomised Trial of an Intensive Physical Therapy Program for Patients with Acute Respiratory Failure. *Am J Respir Crit Care Med* 2016; 193 (10):1101-10.
 19. Phillips BA, Mastaglia FL. Exercise therapy in patients with myopathy. *Curr Opin Neurol* 2000;13:547–552.
 20. Walsh TS, Salisbury LG, Merriweather JL, Boyd JA, Griffith DM, Huby G et al. Increased Hospital-Based Physical Rehabilitation and Information Provision After Intensive Care Unit Discharge The RECOVER randomised Clinical Trial. *JAMA Internal Medicine* 2015; 175 (6): 901-10.

IPHIVAP

IPHIVAP investigators of the Australian and New Zealand Intensive Care Society Clinical Trials Group. Is inhaled prophylactic heparin useful for prevention and management of pneumonia in ventilated ICU patients? J Crit Care 2016;35:231–9

Introduction

Ventilator-associated pneumonia (VAP) affects 9.3% of mechanically ventilated patients and is responsible for half of nosocomial infections in ICU.^{1,2} It is associated with an increase in duration of mechanical ventilation of 9.6 days, ICU stay of 6.1 days and hospital admission of 11.5 days.² Although it is associated with significant morbidity, there is conflicting evidence whether VAP increases mortality; studies have reported an increased risk ratio of mortality of 1.7 to 4.4, whereas others have reported no mortality increase whatsoever.¹⁻³ In the United States of America the morbidity associated with VAP translates to an approximately 40% increase in billed hospital charges.² Indeed, VAP is used as a surrogate marker for quality of care.^{4,5} For all these reasons clinicians apply care bundles to reduce VAP incidence and researchers seek interventions to decrease the risk of VAP.⁶

The definition of VAP published by the National Healthcare Safety Network of the Centres for Disease Control and Prevention (CDC) assesses patients based on three domains; systemic evidence of infection, pulmonary signs (including sputum), and chest radiography changes.⁴ However, the subjective nature of these criteria results in inter-observer variability and large differences in the rates of VAP being reported from 8% to 28%.¹

Unfractionated heparin (UFH) results in dose dependant inhibition of streptococcus pneumoniae and haemophilus influenza growth in vitro and may limit bacterial adhesion within the respiratory tract.^{7,8} It has also been shown to limit neutrophil chemotaxis, lymphocyte activation and mast cell degranulation.⁹ Ventilation induces inflammation and subsequent fibrin deposition within the lung microcirculation and alveolar sacs, promoting ventilation / perfusion mismatch. This may be ameliorated by nebulised heparin.⁸

The anti-inflammatory and antimicrobial properties of heparin have led researchers to use nebulised UFH in a number of conditions. Heparin reduces changes in airway conductance in exercise induced asthma.¹⁰ Indeed, in a single-centre study, nebulised heparin increased ventilator-free days.⁸ Retrospective evidence also suggests nebulised UFH improves respiratory mechanics and oxygenation and reduces re-intubation rates after smoke inhalation injury, though the quality of this evidence is poor.¹¹⁻¹³ On the basis of this evidence, the authors of the IPHIVAP study hypothesised that nebulised heparin may reduce VAP and ventilator-associated complications in mechanically ventilated patients.



Study synopsis

This phase 2, double-blind, randomised controlled trial was designed as a feasibility study to look at the effects of nebulised UFH on mechanically ventilated patients. Patients from three university affiliated ICUs were randomised to one of three groups. The intervention consisted of 5000 units UFH in 2mL nebulised 6 hourly (heparin group). This was compared to either a placebo of 2 mL 0.9% sodium chloride nebulised 6 hourly (sodium chloride group) or a usual care group. Clinicians and investigators were blinded as to which study drug was being nebulised but they were aware of those allocated to usual care. The usual care group were not permitted to receive nebulised sodium chloride or heparin but all groups could receive nebulised steroids or bronchodilators. The intervention was continued until the patient was liberated from invasive mechanical ventilation for > 48 hours or discharged from ICU.

In this pragmatic trial, elements of care such as ventilation mode, ventilator settings, nebuliser type, and humidification were not standardised but best practice was encouraged. Antimicrobial interventions were at the discretion of the treating clinicians with decisions being made in conjunction with unit policy and antimicrobial results.

Adult patients were eligible if they were expected to be mechanically ventilated for > 48 hours. However, they were required to be recruited and the intervention commenced within the first 24 hours of ventilation. Therapeutic anticoagulation was a contraindication to enrolment, though use of heparins for prevention of thromboembolism or to facilitate renal replacement therapy was permitted. Other exclusion criteria included contraindications to subcutaneous heparin, moribund state, treatment limitations, and pregnancy.

The primary end points in relation to VAP were incidence, severity and time to development. This was assessed using the "Klompas Criteria", a modification of the Centres for Disease Control and Prevention (CDC) criteria which allows electronic screening of patient data to identify new cases of VAP (see "where it sits in the body of evidence" for details).⁴

Secondary endpoints included;

- Ventilator Associated Complications (VAC) defined as an increase in PEEP by > 2.5 cmH₂O or FiO₂ by ≥ 15% for ≥ 2 days after the patient had achieved stable or falling PEEP or FiO₂ for ≥ 2 days.³ This was only assessed at the lead site.
- Pneumonia outcomes; clinical resolution, cure, and therapy failure. The definitions of which were provided in the supplementary material and included assessments of PaO₂ / FiO₂ ratio, temperature, secretions, inflammatory markers and chest X-ray.
- Microbiological outcomes; eradication, persistent infection, pneumonia recurrence and superinfection. This assessment was based on endotracheal aspirate cultures



taken on admission and twice weekly thereafter.

- SOFA scores in those who developed VAP or who had pneumonia on admission.

Assuming a VAP rate of 12%; the trial required 277 patients per group to detect a 50% reduction in the incidence of VAP with a 80% power and a significance level of 0.05. To account for patient loss, the authors predicted they would need to recruit 914 patients. These numbers also provided adequate power to detect a reduction in bacterial colonisation from 80% to 40% using the same power and significance levels. Intention-to-treat analysis was performed. There was stratification for study centre and patient type (non-operative or post-operative). The trial was terminated early on the grounds of futility as the observed VAP rate was approximately 6 - 7% in all groups. The authors estimated that 22,000 patients would be required to detect a 1% reduction in VAP.

A total of 2103 patients were screened with 214 being enrolled, 202 were from a single-centre. Patients were excluded predominantly for two reasons; contraindications to subcutaneous heparin (956) and expected to be extubated within 48 hours (514). The three groups were well balanced with the exception of pneumonia on admission, which was more common in the sodium chloride group (56%) than the other two groups (both 35%). This is reflected in the higher use of antibiotics in the sodium chloride group (80%) than in the heparin (61%) and usual care groups (67%), $P=0.03$. The median Clinical Pulmonary Infection Score was 7.4 and almost two thirds of patients with pneumonia on admission had a causative organism identified, with gram negative (22.6%) and *Staphylococcus aureus* (16.6%) being the commonest organisms. The median duration of ventilation was 5.5 days. The overall ICU mortality was 8% despite a mean APACHE II score of 18.9.

There was no difference in the primary outcome measure of progression to VAP using the Klompas criteria; Heparin (7%), sodium chloride (6%), usual care (7%), $P=1.00$.⁴ The time to onset of VAP did not differ between the three groups (median 7 days, $P = 0.35$). When the authors looked at the use of clinical diagnosis, the rate of moderate / high likelihood VAP was 26% and again did not differ between the three groups ($P = 0.85$).

There was no difference in the secondary outcome of VAC; heparin (38%), sodium chloride (28%), usual care (32%), $P=0.59$. The rates of new bacterial colonisation did not differ significantly between the three groups ranging from 42% to 49%, $P=0.70$. There was no difference in rates of gram positive, gram negative, fungi / yeasts between the groups.

Study critique

This phase II study has a number of strengths. The outcome measures chosen in relation to the development of VAP, VAC and microbiological outcomes have previously been validated.³⁻⁵ The study was appropriately blinded; the use of two placebo groups (a usual

care group and a nebulised sodium chloride group) helped take into account the effect that additional nebulisation may have on the incidence of VAP or VAC. Finally, there were a number of safety measures to ensure patients did not come to harm from nebulised UFH.

Rate of resolution of pneumonia was named as a secondary outcome. A potential confounding variable was introduced by recruiting 42% of patients with pneumonia. However, patients required resolution of the incident pneumonia, new onset of sepsis and the identification of a new pathogen before VAP could be diagnosed (personal correspondence with the author; Robert Boots, Brisbane, Australia). Furthermore, patients admitted with pneumonia at baseline were no more likely to go on to develop VAP, this somewhat alleviates concerns regarding this confounding variable.

The criteria chosen to define resolution of pneumonia was taken from a small study of 95 patients with VAP, but no other form of pneumonia.¹⁴ The presence of two of the following empirically chosen criteria at 72 hours was felt to represent resolution of VAP; maximum temperature $\leq 38^{\circ}\text{C}$, $\text{PaO}_2 / \text{FiO}_2$ ratio < 250 mm Hg, white cell count $< 10,000 \times 10^9/\text{L}$, resolution of purulent secretions and ≤ 1 segment with infiltrates on CXR (out of 6 segments). However, only 74.4% of patients had resolution of ≥ 2 of these criteria after 72 hours of appropriate antibiotic therapy and the six criteria did not perform equally. The implications of this on the IPHIVAP trial are unclear.

One of the secondary outcome measures, VAC, was only assessed at a single site. However, this was essentially a single-centre study with 202 of the 214 patients being taken from one unit. There are indicators that this was a high performing unit with an ICU and hospital mortality of 8% and 16% respectively, despite a mean APACHE II score of 18.9. This would have limited the generalisability of any findings, and may have affected the design of any subsequent phase III trial.

The authors powered the study based on an ambitious 50% relative reduction in incidence of VAP. The trial was terminated early due to futility, so ultimately it was underpowered. The results from the primary and secondary outcomes were consistently negative with no signal of benefit or harm reassuring the reader this probably was futile. The authors estimated that 22,000 patients would be needed to detect a 1% reduction in incidence of VAP from 6% to 5%. The authors were only able to recruit 10% of the patients screened, on this basis a study screening 220,000 seems highly unlikely even in the context of an international trial using cluster randomisation. In contrast the application of ventilator care bundles, which are applicable to many more ICU patients, can reduce the relative risk of VAP by 45%.⁶

There was a reasonable biological rationale for the use of nebulised UFH; its antimicrobial properties may reduce VAP and its potential to improve ventilation /



perfusion matching and pulmonary compliance may lead to less injurious ventilation and a reduction in VAC.⁷⁻¹³ However, closer inspection of the evidence calls into question the strength of this rationale. UFH showed inhibition of streptococcus pneumoniae and haemophilus influenza growth in vitro, these two pathogens account typically for approximately 14% of VAP, though in the IPHIVAP trial they accounted for 22% of VAP organisms.^{1,7} However, UFH does not limit growth of acinetobacter baumannii, candida albicans, klebsiella pneumonia, MRSA or pseudomonas aeruginosa which are responsible for over half of VAP cases.^{1,7}

The inhibition of bacterial growth in vitro requires between 2,500 units and 7,500 units per 200 µL for streptococcus pneumoniae and 7,500 units per 200 µL for haemophilus influenza.⁷ Studies of nebulised ^{99m}technetium-labeled sodium heparin demonstrates that only 8 ± 2% of administered drug reaches the lower respiratory tract.¹⁵ Even though it is unclear whether the total dose or concentration is the deciding factor in inhibition of growth, the dose used in this study falls somewhat short. Given that only 0.76 ± 0.35% of the nebulised dose reaches the blood stream, the authors could have safely given a higher dose.¹⁵ The CHARLI study used a dose of 25,000 units safely in mechanically ventilated patients.⁸

There was no standardisation in the type of nebuliser used; higher rates of jet nebuliser were used in the heparin group, in contrast vibrating sieving mesh nebulisers were more common in the sodium chloride group. The authors provide no measure of drug delivery except APTT. This is compounded by the fact that only 74% and 70% of the heparin and sodium chloride groups respectively received the study drug on > 90% of the study days.

Overall this was an interesting phase II study, as it was terminated early it was underpowered. Nebulised UFH has shown some promise by improving respiratory mechanics in mechanically ventilated patients and in the treatment of smoke inhalation injury.⁸⁻¹³ However, the biological rationale behind its use in prevention of VAP is flawed and it seems that ventilator care bundles will remain the therapy of choice.⁶

Where this sits in the body of evidence

The Klompas criteria for diagnosis of VAP was developed in a single-centre study. A computer algorithm was applied to data from 459 patients and 2540 ventilator days. This initially identified patients who met defined levels of increased in PEEP or FiO₂. Those identified were further screened for CXR changes, changes in inflammatory markers and presence of neutrophils in sputum from tracheal aspirate or bronchoalveolar lavage. The 20 patients detected by the electronic method all met CDC criteria (100% positive predictive value). In the comparator group, clinicians were asked to identify cases of clinically suspected VAP. The positive predictive value of clinician assessment was just 52%. The completeness of known cases identified by each method was 95% and 81% for the computer and clinician identified cases respectively (as not all patients were



screened using the CDC criteria, the term sensitivity could not be used).⁴

A large study, involving 61 ICUs, the majority of whom used the CDC definition of VAP, looked at the application of four interventions (peptic ulcer disease prophylaxis, deep vein thrombosis (DVT) prophylaxis, elevation of the head of the bed and sedation vacation) as part of a ventilator bundle. Completion of all four components (unless medically contraindicated) was required for patients to be deemed compliant. The average decrease in VAP rate was 44.5%. In the 21 units where ventilator bundle compliance was $\geq 95\%$ the incidence of VAP decreased from 6.6 to 2.7 per 1,000 ventilator days (difference, 3.9; 95% CI, 1.8 to 5.9; $P < 0.001$).⁶

In a seminal paper by Drakulovic and colleagues; a single-centre, randomised, controlled trial of 87 mechanically ventilated patients randomised participants to supine or semi-recumbent position. 8% of those in the semi-recumbent group developed VAP compared to 34% in the supine group, $P = 0.003$. In keeping with the theory that aspiration was the cause of many cases of VAP, enteral nutrition was an independent risk factor for VAP (OR, 5.7; 1.5 to 22.8; $P = 0.013$).¹⁶

A meta-analysis of three trials ($n = 337$) looking at supine versus semi-recumbent position (45°) demonstrated the latter reduced the risk of developing VAP (OR=0.47; 95% CI, 0.27 to 0.82).¹⁷

Daily sedation vacations are included in the ventilator care bundle, however the original trial contained no measure of VAP in its outcome measures.^{6,18} 150 patients were randomised to sedation with propofol or midazolam infusions with all patients receiving morphine infusion. Patients were then allocated to receive usual care or a daily sedation hold. The sedation hold group had a shorter duration of mechanical ventilation; 4.9 days (IQR, 2.5 to 8.6) vs 7.3 days (IQR, 3.4 to 16.1) ($P = 0.004$). This translated to a decreased duration of ICU stay 6.4 days vs 9.9 days ($P = 0.02$).¹⁸

Selective oropharyngeal tract decontamination (SOD) (topical application of tobramycin, colistin, and amphotericin B) was compared to selective digestive tract decontamination (SDD) (SOD plus 4 days of intravenous cefotaxime) in a cluster randomised, crossover trial involving 5939 mechanically ventilated adults. There was also a usual care group. There was no difference in the primary outcome measure of crude 28 day mortality; standard care, 27.5%; SOD, 26.6%; SDD 26.9%. However, after logistic regression, there was a decreased risk of mortality in both the SOD group (OR, 0.86; 95% CI, 0.74 to 0.99) and SDD group (OR, 0.83; 95% CI, 0.72 to 0.97). Both SDD and SOD reduced the incidence of bacteraemia and the rates of resistant bacteria cultured from respiratory tract specimens.¹⁹

In a trial of 934 ICU patients, SDD was compared to standard care. ICU mortality was lower in patients treated with SDD (15%) than those treated with standard care (23%)



(relative risk, 0.65; 95% CI 0.49 to 0.85, P = 0.002). SDD was associated with a reduction in acquired pseudomonas aeruginosa and gram-negative aerobic bacteria (relative risk 0.61; 95% CI 0.46 to 0.81). There was no difference in rates of vancomycin-resistant enterococcus or methicillin-resistant staphylococcus aureus.²⁰

The CHARLI study was a single-centre, randomised controlled trial, in which 50 patients expected to be ventilated for > 48 hours were randomised to receive nebulised heparin 25,000 units or saline placebo 4-6 times per day. There was no difference in the primary outcome measure of average daily PaO₂ / FiO₂ ratio (194.2 ± 62.8 vs 187 ± 38.6 mm Hg; mean difference, 7.2; 95% CI -22.8 to 37.1, P = 0.6). Among the secondary outcomes, the heparin group exhibited an increase in ventilator-free days in survivors at day 28 (22.6 ± 4.0 vs 18.0 ± 7.1; difference, 4.6; 95% CI, 0.9 to 8.3; P = 0.02).⁸

A single-centre, retrospective, case-control study examined adults with bronchoscopy confirmed smoke inhalation injury. Fourteen cases who were given nebulised UFH, N-acetylcystine and albuterol were compared to 16 historical controls. During the first week, mean lung injury score was lower in cases than controls; 0.91 ± 0.14 vs 1.79 ± 0.41, P = 0.01. The treatment group also had a lower mortality (relative risk, 0.854).¹¹

Should we use nebulised heparin for the prevention of VAP or VAC?

No. There is no benefit from nebulised heparin in prevention of VAP or VAC

References

1. Chastre J, Fagon J-Y. Ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 2002;165(7):867–903.
2. Rello J, Ollendorf DA, Oster G, Vera-Llonch M, Bellm L, Redman R, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large us database*. *Chest.* 2002;122(6):2115–21.
3. Klompas M, Khan Y, Kleinman K, Evans RS, Lloyd JF, Stevenson K, et al. multi-centre Evaluation of a Novel Surveillance Paradigm for Complications of Mechanical Ventilation. *PLOS ONE.* 2011;6(3):e18062.
4. Klompas M, Kleinman K, Platt R. Development of an algorithm for surveillance of ventilator-associated pneumonia with electronic data and comparison of algorithm results with clinician diagnoses. *Infect Control Hosp Epidemiol.* 2008;9(1):31–7.
5. Hayashi Y, Morisawa K, Klompas M, Jones M, Bandeshe H, Boots R, et al. Toward Improved Surveillance: The Impact of Ventilator-Associated Complications on Length



- of Stay and Antibiotic Use in Patients in Intensive Care Units. *Clin Infect Dis*. 2013;56(4):471–7.
6. Resar R, Pronovost P, Haraden C, Simmonds T, Rainey T, Nolan T. Using a Bundle Approach to Improve Ventilator Care Processes and Reduce Ventilator-Associated Pneumonia. *Joint Commission Journal on Quality and Patient Safety*. 2005;31(5):243–8.
 7. Zappala C, Chandan S, George N, Faoagali J, Boots RJ. The antimicrobial effect of heparin on common respiratory pathogens. *Crit Care Resusc*. 2007;9(2):157–60.
 8. Dixon B, Schultz MJ, Smith R, Fink JB, Santamaria JD, Campbell DJ. Nebulized heparin is associated with fewer days of mechanical ventilation in critically ill patients: a randomised controlled trial. *Crit Care*. 2010;14(5):R180.
 9. Yildiz A, John E, Özsoy Y, Araman A, Birchall JC, Broadley KJ, et al. Inhaled extended-release microparticles of heparin elicit improved pulmonary pharmacodynamics against antigen-mediated airway hyper-reactivity and inflammation. *Journal of Controlled Release*. 2012;162(2):456–63.
 10. Ahmed T, Garrigo J, Danta I. Preventing bronchoconstriction in exercise-induced asthma with inhaled heparin. *N Engl J Med*. 1993;329(2):90–5.
 11. Miller AC, Rivero A, Ziad S, Smith DJ, Elamin EM. Influence of nebulized unfractionated heparin and N-acetylcysteine in acute lung injury after smoke inhalation injury. *J Burn Care Res*. 2009;30(2):249–56.
 12. Desai MH, Mlcak R, Richardson J, Nichols R, Herndon DN. Reduction in mortality in pediatric patients with inhalation injury with aerosolized heparin/N-acetylcysteine [correction of acetylcysteine] therapy. *J Burn Care Rehabil*. 1998;19(3):210–2.
 13. Otremba S, Faris J, Zimmerman LH, Barbat S, White, M. 923: Inhaled heparin in critically ill patients with smoke. *Crit Care Med* 2013;41(12) Supplement: A231-2
 14. Vidaur L, Gualis B, Rodriguez A, Ramírez R, Sandiumenge A, Sirgo G, et al. Clinical resolution in patients with suspicion of ventilator-associated pneumonia: a cohort study comparing patients with and without acute respiratory distress syndrome. *Crit Care Med*. 2005;33(6):1248–53
 15. Bendstrup KE, Chambers CB, Jensen JI, Newhouse MT. Lung Deposition and Clearance of Inhaled ^{99m}Tc-Heparin in Healthy Volunteers. *Am J Respir Crit Care Med*. 1999;160(5):1653–8.
 16. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogué S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *The Lancet*. 1999;354(9193):1851–8.
 17. Alexiou VG, Ierodiakonou V, Dimopoulos G, Falagas ME. Impact of patient position on the incidence of ventilator-associated pneumonia: A meta-analysis of randomised controlled trials. *Journal of Critical Care*. 2009;24(4):515–22.



18. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily Interruption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation. *New England Journal of Medicine*. 2000;342(20):1471–7.
19. de Smet AMGA, Kluytmans JAJW, Cooper BS, Mascini EM, Benus RFJ, van der Werf TS, et al. Decontamination of the Digestive Tract and Oropharynx in ICU Patients. *New England Journal of Medicine*. 2009;360(1):20–31.
20. Jonge E de, Schultz MJ, Spanjaard L, Bossuyt PM, Vroom MB, Dankert J, et al. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *The Lancet*. 2003;362(9389):1011–6.



LUNG SAFE

Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA. 2016 Feb 23;315(8):788–800.

Introduction

In 2012, the Acute Respiratory Distress Syndrome (ARDS) definition task force redefined ARDS providing an update on the 1994 American-European Consensus Conference (AECC) definition.^{1,2} The task force presented a conceptual model for ARDS, describing it as an acute lung injury where inflammation causes increased vascular permeability and loss of aerated lung tissue resulting in shunt, dead space and decreased lung compliance. The clinical manifestation of this is hypoxaemia, difficulty with ventilation and bilateral pulmonary infiltrates.¹ To diagnose ARDS, patients must fulfil the criteria of; acute onset respiratory failure (within one week of insult), a PaO₂/FIO₂ ratio ≤ 300 mm Hg, and bilateral opacities on chest imaging all of which is not fully explained by cardiac failure or fluid overload.¹

A number of studies have been conducted into the epidemiology of ARDS using the AECC definition.³⁻⁶ The incidence of ARDS in mechanically ventilated patients has been similar worldwide; 16.1% in Europe, 17.8% in America and 19% in Ireland.³⁻⁵ However, the quoted incidence on a *population basis* ranges from 7.2/100,000 population/year in Spain to 86.2/100,000 population/year in America.^{4,6}

Previous epidemiological studies have used a process of manual screening, performed by physicians, nurses or respiratory therapists, to identify cases of ARDS using the AECC definition.²⁻⁴ This definition has been shown to have moderate sensitivity (0.83, 95% CI 0.72 to 0.95) but poor specificity (0.51, 95% CI 0.41 to 0.61) in comparison to autopsy findings of mechanically ventilated patients.⁷

Given the variation in the global incidence of ARDS and the poor performance of the AECC definition, a large scale epidemiological study using the revised Berlin definition was warranted.

Study synopsis

The LUNG SAFE study was an international, multi-centre, prospective cohort study which set out to assess the epidemiology, clinician recognition and management interventions used in ARDS. Participating ICUs were recruited through relevant societies and networks resulting in a convenience sample of ICUs. Patients were enrolled during four consecutive winter weeks, which were selected by each ICU (February to March 2014 in the Northern hemisphere and June to August 2014 in the Southern hemisphere).



In participating ICUs, all patients aged 16 or older who required invasive or non-invasive mechanical ventilation were enrolled. To identify potential cases of ARDS, patients were screened daily looking for the presence of acute hypoxic respiratory failure which required all three of the following criteria; $\text{PaO}_2/\text{FIO}_2 \leq 300$ mm Hg, need for CPAP, EPAP or PEEP ≥ 5 cmH₂O and new pulmonary infiltrates on chest imaging. Once potential cases were identified, a computer algorithm applied the Berlin Definition to identify true cases of ARDS. On Day 1 (i.e. the time of diagnosis of ARDS using the computer algorithm), clinicians were asked if the patient had ARDS. On exit from the study, clinicians were asked of the patient had ARDS at any point during their ICU stay. Although clinicians were offered a CXR training module they were not prompted to use the Berlin Definition.

The primary outcome measure was incidence of ARDS in the ICU. The severity of ARDS was based on the $\text{PaO}_2/\text{FIO}_2$ ratio on the first day of diagnosis. Secondary outcomes measures included rates of clinician recognition of ARDS, management interventions used and patient outcomes including mortality. The authors wished to enrol 1000 patients as, assuming a 30% mortality, this would give the 300 deaths needed to carry out the planned multivariate analysis. The incidence of ARDS was assumed to be 5% of all ICU admissions, therefore 20,000 patients would need to be enrolled. To achieve this, the authors targeted recruitment of 500 medium-sized ICUs admitting 50 patients per month. All P values used were 2-sided, values < 0.05 considered to be statistically significant.

29,144 patients were admitted to the 459 participating ICUs during the study period, 13,566 received invasive or non-invasive ventilatory support and 12,906 had a complete dataset. On screening, 4,499 patients had acute hypoxaemic respiratory failure, with 3,022 (67.2%) fulfilling the Berlin Definition of ARDS. The incidence of ARDS was 10.4% (95% CI, 10.0% to 10.7%) of all ICU admissions and 23.4% (95% CI, 21.7% to 25.2%) of all mechanically ventilated patients. 93.1% of patients who developed ARDS did so on day one or two of their acute hypoxic respiratory failure. The mean age of ARDS patients was 61.5 years, 62% were male, and 59.4% had pneumonia. The median duration of mechanical ventilation was 8 days (IQR 4 to 16), the median ICU length of stay was 10 days (IQR 5 to 19) and median hospital length of stay was 17 days (IQR 9 to 32). The ICU survival was 66.0% (95% CI, 64.3% to 67.7%) and hospital survival was 60.4% (95% CI, 58.7% to 62.2%).

To achieve a homogenous population, the authors present data from patients who were invasively mechanically ventilated who developed ARDS on day one or two ($n = 2377$). From this group, data is presented on severity of ARDS, ventilator settings, and patient outcomes.

Using the Berlin Definition of ARDS severity; 30.0% of cases were mild, 46.6% of cases

were moderate, and 23.4% of cases were severe. 60.2% of ARDS cases were clinician recognised; recognition was more likely for severe ARDS 78.5% (95% CI, 74.8% to 81.8%) than for mild ARDS 51.3% (95% CI, 47.5% to 55.0%). At the time of fulfilment of ARDS criteria only 34.0% was recognised by clinicians pointing towards diagnostic delay.

On the first day of ARDS, 63.7% of the patients received lung protective ventilation (tidal volume \leq 8 mL/kg predicted body weight (PBW) and plateau pressure \leq 30 cmH₂O). 35.1% (95% CI, 33.1% to 37.1%) of patients with ARDS received tidal volumes $>$ 8 mL/kg PBW. Tidal volumes were lower in patients with physician recognised ARDS (7.5 mL/kg PBW; 95% CI, 7.4 to 7.6 mL/kg PBW) compared to those whose ARDS was not recognised (7.7 mL/kg PBW; 95% CI, 7.6 to 7.9 mL/kg PBW) ($P=0.01$). However, after multivariable analysis of patient and organisational factors, this was no longer statistically significant ($P = 0.08$).

PEEP was higher in those with physician recognised ARDS compared to those whose ARDS was not recognised; 8.9 cmH₂O vs 7.5 cmH₂O ($P < 0.001$). In patients with severe ARDS, the mean PEEP was 10.1 cmH₂O (95% CI, 9.8 to 10.4). However, there was no relationship between PEEP and PaO₂/FIO₂ or FiO₂ but an inverse relationship between FiO₂ and SpO₂. This suggests hypoxia was managed with increased oxygen not PEEP.

In patients with severe ARDS, prone positioning was used in 16.3% (95% CI, 13.7% to 19.2%), neuromuscular blockade in 37.8% (95% CI, 34.1% to 41.2%) and high dose corticosteroids 23.3% (95% CI, 20.3% to 26.6%). In comparison to other ARDS severity categories, patients with severe ARDS were more likely to receive continuous neuromuscular blockade ($P < 0.001$), prone position ($P < 0.001$), recruitment manoeuvres ($P < 0.001$), ECMO ($P < 0.001$) and corticosteroids ($P < 0.001$).

The following hospital mortality rates were observed; mild ARDS, 34.9% (95% CI, 31.4% to 38.5%); moderate ARDS, 40.3% (95% CI, 37.4% to 43.3%); severe ARDS, 46.1% (95% CI, 41.9% to 50.4%). Patients who had a driving pressure $>$ 14 cmH₂O had a higher mortality than those who had a driving pressure of \leq 14 cmH₂O ($P=0.02$). However, driving pressure could only be calculated in the 40.1% of patients who had plateau pressure reported.

Study critique

This prospective, observational, cohort study has a number of strengths. As a multinational trial drawing patients from 50 countries and a range of ICU sizes (median number of beds 13 [IQR 9-20]) it provides data that should be widely generalisable. Data collection was robust; incomplete patient electronic case report forms were excluded, data was screened and potentially erroneous data was verified or corrected and no assumptions were made for missing data. In addition, the data collected allowed ARDS to be defined in keeping with the new Berlin Definition.¹ The screening of patients for



ARDS using a computer algorithm also identified many more patients than clinicians.

The greatest criticism of this dataset is that it came from a convenience sample of ICUs made up of interested parties. The selective nature of this dataset is exemplified by the fact that 207 of 666 initially interested ICUs either did not enrol any patients or withdrew voluntarily therefore being excluded from the final analysis. As such, it may overestimate the clinician recognition of ARDS and how well management strategies for ARDS were applied. Furthermore, a web-based training package was offered to site investigators in an effort to improve recognition of ARDS, this intervention potentially introduced a confounding variable to this observational study.

The use of just four weeks during the “winter” (February and March were selected in the Northern Hemisphere) may mean that the incidence of ARDS is overestimated or that ARDS due to seasonal influenza is overrepresented.⁸ Another criticism is the exclusion of a large number of patients from the analyses of severity, ventilator management and outcome. These included 436 patients who required non-invasive ventilation initially (136 of these went on to require invasive mechanical ventilation) and of 209 mechanically ventilated patients who developed ARDS after day two of their acute hypoxia respiratory failure.

The most striking finding of this study is the failure of implementation of evidence based ventilatory strategies accompanied with use of adjunctive treatments that are ineffective or harmful. 35% of patients with ARDS received tidal volumes > 8 mL/kg PBW and approximately 60% received a tidal volumes > 7 mL/kg PBW. ARDS was consistently under diagnosed and often diagnosed late. However, physician recognition did little to improve the management with no statistically significant reduction in tidal volumes. It could be argued that physician recognition of ARDS should not be a prerequisite or barrier to lung protective ventilation. Ventilation with 6 ml/kg PBW in patients without lung injury has been shown to reduce the number of patients who go on to develop ARDS (P = 0.01).⁹

Although PEEP was statistically higher in patients where ARDS was physician recognised, the difference may have been of little clinical significance (8.9 cmH₂O versus 7.5 cmH₂O (P < 0.001)). In severe ARDS, PEEP rarely reached levels seen in high PEEP trials.¹⁰ In patients on FiO₂ 1.0, the median PEEP was just 10 cmH₂O. Low tidal volume ventilation and high PEEP in severe ARDS have consistently been shown to reduce mortality, yet these ventilation strategies were inconsistently applied.^{10,11}

In patients with severe ARDS, the use of adjuvant therapies was low, prone positioning was used in 16.3% and neuromuscular blockade in 37.8%. However, prone positioning and neuromuscular blockade were used in scores of patients categorised as having mild or moderate ARDS. These therapies have been shown to benefit patients with a



PaO₂/FiO₂ of < 150 mm Hg and it is unclear from this study whether they were used appropriately.^{12,13} ARDS severity was categorised based on the PaO₂/FiO₂ on the first day of diagnosis. Of the patients who had an initial diagnosis of mild ARDS, 25.8% progressed to moderate and 4.5% progressed to severe ARDS. Nevertheless, in a number of cases, patients were managed with ineffective therapies; 7.7% of patients had inhaled pulmonary vasodilators, 28 patients received high frequency oscillatory ventilation.

The authors state that the low use of adjunctive therapies (in appropriate patients) such as neuromuscular blockade may represent doubt among clinicians as to the quality of evidence. However, three findings go against this; these therapies may have been applied in the incorrect patient cohort, therapies for which there is evidence of harm continue to be applied, and lung protective ventilation strategies for which there is an established body of evidence were not applied. This suggests that there are other barriers to implementation of appropriate treatments for ARDS.

Despite the minor criticisms of the study above, this paper provides a valuable insight into the epidemiology and management of ARDS. Worryingly, the 40.0% hospital mortality seen in this observational study was similar to the 39.8% 180 day mortality seen in the 12ml/kg *control group* in the original ARDSnet trial.¹¹ This paper emphasises the need for clinicians to diagnose ARDS promptly and apply ventilatory strategies and adjunctive therapies appropriately to save lives.

Where this sits in the body of evidence

The ARDSNet group conducted a trial comparing lung protective ventilation (VT 6ml/kg PBW, Plateau pressure (Pplat) < 30 cmH₂O) versus conventional ventilation (VT 12ml/kg PBW, Pplat < 50 cmH₂O). Patients managed with lung protective ventilation had a lower 180 day mortality (31.0%) than those managed with conventional ventilation (39.8%) (P = 0.007). Lung protective ventilation also resulted in a greater number of ventilator-free days in the first 28 days after randomisation 12 ± 11 vs 10 ± 11 (P = 0.007). The major criticism of this paper related to the large tidal volumes used in the control group.¹¹

A trial of lung protective ventilation in patients without lung injury compared ventilation with 10 ml/kg PBW (conventional ventilation group) with 6 ml/kg PBW (lung protective group). 13.5% of the conventional ventilation group went on to develop ARDS compared to 2.6% in the lung protective group (P=0.01).⁹

549 patients with ARDS (PaO₂:FiO₂ < 300 mm Hg) were recruited into a trial comparing high versus low PEEP in addition to lung protective ventilation. Mean PEEP values were 8.3 ± 3.2 cmH₂O in the low PEEP group compared to 13.2 ± 3.5 cmH₂O in the higher-PEEP group (P < 0.001). In-hospital mortality was 24.9% and 27.5% respectively (P=0.48).¹⁴



A meta-analysis examining the effect of PEEP on mortality in patients with ARDS found high PEEP (in conjunction with lung protective ventilation) to be beneficial in patients with a PaO₂:FiO₂ ratio < 200 mm Hg. The in-hospital mortality was 34.1% in the high PEEP group vs 39.1% in the low PEEP group (adjusted relative risk, 0.90; 95% CI, 0.81 to 1.00; P=0.049). In patients with a PaO₂:FiO₂ ratio 200 to 300 mm Hg in hospital mortality was 27.2% in the high PEEP group vs 19.4% in the low PEEP group (adjusted RR, 1.37; 95% CI, 0.98 to 1.92; P=0.07).¹⁰

The PROSEVA study looked at prone positioning for 16 hours per day in patients with ARDS with a PaO₂:FiO₂ of < 150 mm Hg. The 28-day mortality was significantly lower in the prone group 16.0% vs 32.8% (P < 0.001) (hazard ratio for death, 0.39; 95% CI 0.25 to 0.63).¹²

340 patients who required mechanical ventilation for ARDS and had a PaO₂:FiO₂ ratio of < 150 mm Hg were randomised to receive 48 hours of cisatracurium or placebo. There was no difference in the crude 90-day mortality; 31.6% in the cisatracurium group compared to 40.7% in the placebo group (P=0.08). At baseline the PaO₂:FiO₂ ratio was significantly lower in the cisatracurium group (106 ± 36) than the placebo group (115 ± 41) (P = 0.03). After adjustment for PaO₂:FiO₂, Pplat, and Simplified Acute Physiology II score, a significantly lower 90 day mortality was seen in the cisatracurium group (Hazard Ratio, 0.68; 95% CI, 0.48 to 0.98; P=0.04).¹³

The use of high frequency oscillatory ventilation (HFOV) was compared to lung protective ventilation in patients with ARDS and a PaO₂:FiO₂ < 200 mm Hg. HFOV was associated with a higher in hospital mortality (47%) than the control group (35%) (relative risk of death with HFOV, 1.33; 95% CI, 1.09 to 1.64; P = 0.005). Vasopressor requirements were also higher on day one in the HFOV group (P < 0.001). The trial was terminated after an interim analysis due to the higher mortality seen in the HFOV group, 548 patients had undergone randomisation at this point.¹⁵

The effect of steroids in ARDS of ≥ 7 days duration was investigated in a trial which randomised 180 patients to placebo or methylprednisolone. The dose of methylprednisolone used was 2 mg/kg PBW loading dose, followed by 0.5 mg/kg PBW 6 hourly for 14 days, then 0.5 mg/Kg PBW 12 hourly, finally a tapering of the dose over 4 days. There was no difference in the primary outcome measure of 60 day mortality; methylprednisolone group 29.2% (95% CI, 20.8% to 39.4%) vs placebo group 28.6% (95% CI, 20.3% to 38.6%) (P=1.0). However, in patients enrolled > 14 days after the onset of ARDS, methylprednisolone was associated with a significantly higher mortality (39.3%) than the placebo (8.8%) (P=0.02).¹⁶

Amato and colleagues conducted an analysis of patients previously recruited into ARDS trials to examine the effect of a number of variables, including driving pressure (ΔP), on



survival. Trials examining the effect of tidal volume interventions were used as part of a derivation cohort, trials into high PEEP were used as a validation cohort. In all patients (irrespective of treatment allocation), a one standard deviation increase in ΔP (equating to 7 cmH₂O) measured at day 1 was associated with increased mortality (relative risk, 1.41; 95% CI, 1.32 to 1.52; P<0.001). When analysing only patients who received lung protective ventilation; those who had a driving pressure less than or equal to the median (13 cmH₂O) had an improved survival than those with driving pressure > 13 cmH₂O (relative risk, 1.36; 95% CI, 1.17 to 1.58; P < 0.001). In mediation analysis ΔP was responsible for 75% of the treatment benefit seen in the tidal volume trials (P = 0.004) and 45% of the benefits seen in the PEEP trials (P = 0.001).¹⁷

Should we implement the results of this trial into our practice?

N/A. ARDS remains a significant problem worldwide.

References

1. The ARDS Definition Task Force*. Acute respiratory distress syndrome: The Berlin definition. *JAMA*. 2012 Jun 20;307(23):2526–33.
2. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994 Mar 1;149(3):818–24.
3. Brun-Buisson C, Minelli C, Bertolini G, Brazzi L, Pimentel J, Lewandowski K, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. *Intensive Care Med*. 2004 Jan;30(1):51–61.
4. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. Incidence and Outcomes of Acute Lung Injury. *N Engl J Med*. 2005 Oct 20;353(16):1685–93.
5. Irish Critical Care Trials Group. Acute lung injury and the acute respiratory distress syndrome in Ireland: a prospective audit of epidemiology and management. *Crit Care*. 2008 Feb 1;12(1):R30.
6. Villar J, Blanco J, Añón JM, Santos-Bouza A, Blanch L, Ambrós A, et al. The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. *Intensive Care Med*. 2011 Dec;37(12):1932–41.
7. Ferguson ND, Frutos-Vivar F, Esteban A, Fernández-Segoviano P, Aramburu JA, Nájera L, et al. Acute respiratory distress syndrome: underrecognition by clinicians and diagnostic accuracy of three clinical definitions. *Crit Care Med*. 2005 Oct;33(10):2228–34.
8. Rothberg MB, Haessler SD. Complications of seasonal and pandemic influenza:

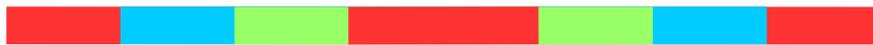


Critical Care Medicine. 2010 Apr;38:e91–7.

9. Determann RM, Royakkers A, Wolthuis EK, Vlaar AP, Choi G, Paulus F, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomised controlled trial. *Crit Care*. 2010;14(1):R1.
10. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: Systematic review and meta-analysis. *JAMA*. 2010 Mar 3;303(9):865–73.
11. The Acute Respiratory Distress Syndrome Network. Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. *N Engl J Med*. 2000 May 4;342(18):1301–8.
12. Guérin C, Reignier J, Richard J-C, Beuret P, Gacouin A, Boulain T, et al. Prone Positioning in Severe Acute Respiratory Distress Syndrome. *N Engl J Med*. 2013 Jun 6;368(23):2159–68.
13. Papazian L, Forel J-M, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010 Sep 16;363(12):1107–16.
14. The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome. *N Engl J Med*. 2004 Jul 22;351(4):327–36.
15. Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, et al. High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome. *N Engl J Med*. 2013 Feb 28;368(9):795–805.
16. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med*. 2006 Apr 20;354(16):1671–84.
17. Amato MBP, Meade MO, Slutsky AS, Brochard L, Costa ELV, Schoenfeld DA, et al. Driving Pressure and Survival in the Acute Respiratory Distress Syndrome. *N Engl J Med*. 2015 Feb 19;372(8):747–55.



GI & Nutrition Trials



PEPaNIC

Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, et al. Early versus Late Parenteral Nutrition in Critically Ill Children. N Engl J Med 2016; 374:1111-1122

Introduction

Nutrition remains an area of great confusion in the intensive care unit. For years the mantra was that no patient could starve him- or her-self back to fitness and aggressive feeding was required to prevent the catabolism which accompanies critical illness. However, this runs contrary to our highly conserved natural response to illness – anorexia. Whether this is simply an inconvenient obstacle to our paradigm of more feeding, or a warning from nature to obey her signs, remains uncertain. What has changed is our willingness to challenge the orthodoxy and dogma of the food first approach.

The past decade in critical care has seen an explosion in reversals of landmark trials¹ and an understanding that we need to explore the basics of critical care provision. The need to feed comes into this category. While clearly all patients require nutrition in the long term, whether they need it in the short term is unclear. Not only is this need unclear, but it may be associated with harm. Early feeding in critical illness is associated with reduced autophagy, a self regulatory process where damaged organelles and proteins, injured during periods of stress, are cleared.²

Against this backdrop of uncertainty, there have been a large number of high quality critical care trials in the area of nutrition over the past number of years. Several have examined the role of parenteral nutrition, although mostly in the adult population.

Study synopsis

PEPaNIC was a tri-centre, randomized, controlled, parallel-group superiority trial investigating whether withholding supplemental parenteral nutrition for up to a week in critically ill paediatric patients at risk for malnutrition is clinically superior to early supplementary parenteral nutrition. Notably, all three centres used early parenteral nutrition as a standard of care.

Eligibility criteria included admission to the ICU with an expected stay of greater than 24 hours, a medium risk of malnutrition {score of 2 or more on the STRONGkids screening tool, which ranges from 0 (low risk of malnutrition) to 5 (high risk)} and aged between term newborn to 17 years. Exclusion criteria included a lack of requirement for nutritional support, a low risk of malnutrition (STRONGkids < 2), a do-not-resuscitate order, imminent death, enrolment in another trial, transfer from another PICU/NICU after a stay of greater than 7 days, ketoacidotic or hyperosmolar coma, inborn error of



metabolism requiring a specific diet or other requirement for parenteral nutrition. Randomisation was performed via a central computerised system, in a blinded 1:1 fashion, stratified in permuted blocks of 10 according to age (<1 year or ≥1 year) and diagnosis on admission (medical–neurological, medical-other, surgical-cardiac, or surgical-other), to either early parenteral nutrition (within 24 hours) or late parenteral nutrition (commenced after 7 days). The dose and constitution of the parenteral nutrition was according to local standards and was not specified. Parenteral nutrition was used to supplement enteral nutrition with the aim of meeting macronutrient and caloric targets.

Enteral nutrition was commenced in both groups as per local practice, which included the provision of intravenous trace elements, minerals, and vitamins, starting from day 2. The late parenteral nutrition group received intravenous fluids (a mixture of 5% dextrose and 0.9% saline) to match the intake volume of the early parenteral nutrition group. On the morning of the 8th day, parenteral nutrition was commenced in the late parenteral group if enteral intake remained below 80% of target caloric feeding, delivered enterally.

Glycaemic management differed across the three centres. In Leuven, Belgium, insulin infusions were used in all children to maintain blood glucose concentrations at 2.8 to 4.4 mmol/l in infants <1 year of age and 3.9 to 5.6 mmol/l in children ≥1 year of age. In Rotterdam, the Netherlands, blood glucose was maintained at 4.0 to 8.0 mmol/l in all children, except in the presence of a traumatic brain injury. In Edmonton, Canada, glycaemic management was similar to standard adult practice, keeping the blood sugar below 10 mmol/l only. Episodes of hypoglycaemia, defined as being below 2.8 mmol/l, were treated by substituting 10% dextrose for 5% dextrose until the blood glucose value stabilised above 4.4 mmol/l.

The two primary endpoints were new ICU-acquired infection and the duration of ICU dependency, which was the number of days spent in PICU. The primary outcomes were adjusted for 5 baseline risk factors. Secondary efficacy endpoints included time to weaning from mechanical ventilation, duration of haemodynamic support, proportion requiring renal replacement therapy, liver dysfunction and time to discharge alive from the hospital. Secondary safety endpoints included death in PICU within the first 7 days, total stays in PICU and hospital, respectively, and hypoglycaemia (< 2.2 mmol/l).

1,440 patients would have 70% power to detect a 5% reduction, from 20% to 15%, of rates of new infection in the late parenteral nutrition group compared to the early group, at a two sided 5% significance level. Analysis was on an intention-to-treat basis.

Over a three year period, from June 2012, 7,519 children were screened and 1,440 randomised, 723 to the early group and 717 to the late group. The most common



reasons for exclusion were a lack of requirement for nutritional support, low risk of malnutrition, readmissions, enrolment in another trial and transfer in from another unit. Groups were similar at baseline and are distinguished by the young age of the participants, with median ages of 1.4 and 1.5 years, in the early and late groups, respectively. Approximately 38% in both groups had undergone cardiac surgery, 87% were receiving mechanical ventilation and 38% had an infection.

Energy provision via the enteral route was similar between groups, including protein, carbohydrate and fat intake, but separated between groups in terms of parenteral nutrition, with the early group achieving higher rates of feeding. The total nutritional intake in the first week was greater in the early parenteral nutrition group.

Late parenteral nutrition resulted in a 7.7% absolute reduction in new ICU-acquired infections (mean±SD; 18.5% vs 10.7%; adjusted OR, 0.48; 95% CI, 0.35 to 0.6; P<0.001). The total duration of stay in PICU was also reduced in the late parenteral nutrition group (9.2±0.8 days vs 6.5±0.4 days; adjusted OR, 1.23; 95% CI, 1.11 to 1.37; P<0.001). Patients in the late group also spent less time on the mechanical ventilator (6.4±0.7 days vs 4.4±0.3 days; aOR, 1.19; 1.07 to 1.32; P=0.04), required less renal replacement therapy (3.6% vs 2.5%; aOR, 0.49; 0.24 to 0.96; P=0.04) and had shorter durations of hospital stay, both in the index hospital and when combined with a transferring hospital. Rates of hypoglycaemia were significantly higher in the late group (4.8% vs 9.1%; P=0.001)

Study critique

This large three centre study in three different countries, Belgium, the Netherlands and Canada, tested whether late supplemental parenteral nutrition was superior to early supplemental parenteral nutrition in children at medium risk for malnutrition.

PEPaNIC robustly addressed the stated hypothesis, within the confines of the study, and has high internal validity. The addition of late supplemental parenteral nutrition appears to have clinical benefits over the early supplementation of parenteral nutrition. Both primary outcomes were in favour of the late group. The trial methodology was of high standard, with clear inclusion and exclusion criteria, computer-based randomisation, excellent separation of the groups with respect to parenteral nutrition and blinded adjudication of the development of new infection in the ICU. The protocol was published during the running of the trial.³ However, as excellently as this trial may have been executed, the question of external validity is much less clear.

Although early supplemental parenteral nutrition is standard practice in each of the three trial centres, to what degree this practice exists outside of these centres is uncertain. Clearly any patient unable to tolerate enteral nutrition will require parenteral nutrition, the question becomes one of “when?”. How long should a clinician wait to see if the patient’s gut starts to function again, allowing recommencement of enteral



feeding. Like two sides of a coin, the question of when to initiate supplementary parenteral nutrition is intrinsically linked with the question of what degree of nutritional insufficiency requires supplementation acutely? Therefore, for a patient receiving some enteral nutrition, does the addition of supplemental parenteral nutrition, allowing closer to 100% of nutritional targets to be met, improve outcome, or simply subject patients to risks from iatrogenesis.

In addition to the unique early supplemental parenteral feeding employed by these three centres, the glycaemic management was also somewhat unusual in two of them. The very tight glycaemic range of just 2.8 to 4.4 mmol/l in infants <1 year of age and 3.9 to 5.6 mmol/l in children \geq 1 year of age in Leuven seems dramatic. However, these glycaemic ranges are both evidence-based and associated with benefit over conventional ranges, when tested in Leuven.¹³ Also, the tolerance of very low glucose levels in very young children appears strange to those unfamiliar with the management of critically ill children. Almost 1 in 10 patients in the late group suffered significant hypoglycaemia (< 2.2 mmol/l). Given the increased mortality seen with hypoglycaemia in the adult NICE-SUGAR trial,⁴ values of 10% suffering blood glucose values this low appear worrying. Although the rates of death were small (early group, 6.8% at day 90 vs late group, 5.3%; aOR, 0.64; 95% CI, 0.39 to 1.05; P=0.08), and the point estimate is non-significantly in favour of the late group, it will be interesting to see if the potential neuroglycopenia has developmental effects in the years to come.

Similar to the original Leuven tight glycaemic control study in adults,⁵ a large percentage of patients, over a third, were recruited from the cardiac surgical setting. Adding this cohort to a general population of emergency PICU admissions creates a large degree of heterogeneity. A further problem is that many of these children would not have received parenteral nutrition in other centres, given the majority were discharged from the ICU after just a few days. Another issue with the chosen population is the use of the STRONGkids malnutrition screening tool, which is unvalidated in critically ill children.¹¹ Few children in the study appear to have been genuinely at risk from malnutrition. When the very young median age is included, then a picture of a unique study forms – unusual feeding, very tight glycaemic control, young age of patients, heterogenous population at low risk of malnutrition receiving an intervention not widely used and which the investigators hypothesise is associated with harm. The external generalisability of this study would suffer markedly if the results didn't sit so well with other adult trials asking similar questions.

A final issue related to the methodology of the trial pertains the choice of primary outcome measures. While the adjudication of the primary outcome of newly acquired ICU-infection was performed in a blinded manner, readiness for discharge was a subjective decision made in the knowledge of group assignment.¹¹



Where this sits in the body of evidence

Doig and colleagues asked a similar, but slightly different question, to that posed by PEPaNIC. They undertook the large multi-centre randomised controlled Early Parenteral Nutrition study, comparing early with late parenteral nutrition in critically ill adults with short-term relative contraindications to early enteral nutrition.⁶ 1,372 patients were randomised across 31 ICUs in Australia and New Zealand. These patients were expected to stay in the ICU for at least 2 days and unable to be fed enterally. Patients in the early parenteral nutrition group commenced parenteral feeding at a mean of 44 minutes after enrolment, while the standard care group commenced feeding, either enteral or parenteral, at a mean of 2.8 days. Early parenteral nutrition resulted in fewer days of invasive mechanical ventilation, but had no effect on length of stay in the ICU or hospital, or mortality at day 60 (22.8% standard care vs 21.5% for early parenteral feeding).

The EPaNIC trial was almost an adult version of the PEPaNIC trial, comparing early parenteral supplementation (within 48 hours) with late parenteral supplementation (after a week) in 4,640 critically ill patients with insufficient enteral nutrition.⁷ Enterally delivered nutrition was similar between groups, but the late parenteral group received less parenteral nutrition. Overall, this translated into less total nutrition delivered over the first week. Patients receiving late parenteral nutrition had a shorter duration of stay in the ICU (median 3 days vs 4 days; $P=0.02$) and were more likely to be discharged alive early from the ICU (HR, 1.06; 95% CI, 1.00 to 1.13; $P=0.04$). This group also had less new infections, lower measures of inflammation and a shorter duration of mechanical ventilation.

A substudy of the EPaNIC trial sought to determine the effects of an early macronutrient deficit on muscle wasting and weakness.⁸ Contrary to commonly-held beliefs that early inadequate nutrition contributes to catabolism and weakness, the late parenteral nutrition group, who received less total nutrition, had less weakness than the early parenteral group at first assessment at day 9. (34% vs 43%, absolute difference -9%; 95% CI, -16 to -1%; $P=0.030$). Myofibre cross-sectional area and density were lower in both the early and late parenteral groups in comparison with healthy controls, but the late group had superior scores to the early group. This was due to more efficient autophagosome formation and clearance of cellular debris.

The SPN randomised controlled trial was a two-centre study from Switzerland comparing enteral nutrition alone with enteral nutrition supplemented with parenteral nutrition in 305 critically ill patients achieving less than 60% of their target calorific feed at day 3.⁹ Groups were similar at baseline and separated well in terms of delivered nutrition over the next five days, with the combined group achieving 28 kcal/kg/day while the enteral only group received 20 kcal/kg/day. The combined group had less nosocomial infections between day 8 and 28 (primary outcome), 27% vs 38%; HR, 0.65; 95% CI, 0.43 to 0.97;



P=0.034. Other clinical outcomes were similar between group.

EDEN was an open-label, multi-centre, randomised controlled trial evaluating deliberate underfeeding in patients with ARDS.¹⁰ 1,000 patients within 48 hours of the identification of ARDS were randomised to receive either full enteral feeding or trophic enteral feeding for the first 6 days. Groups were similar at baseline. The amount of delivered calories differed significantly between groups, 1300 kcal/d vs 400 kcal/d (P<.001). Full feeding resulted in more vomiting (2.2% vs 1.7%; P=0.05), elevated gastric residual volumes (4.9% vs 2.2% of feeding days; P<0.001), and constipation (3.1% vs 2.1% of feeding days; P=0.003). There were no significant differences in other clinical outcomes.

Van den Berghe and colleagues published the first major randomised controlled trial evaluating the role of tight glycaemic control in critically ill adults, comparing a tight maintenance of blood sugars 4.4 to 6.1 mmol/l with a more liberal range, starting when blood glucose exceed 12 mmol/ and targeting a range of 10 and 11.1 mmol/l.⁵ An intravenous insulin infusion was used to achieve these blood sugar ranges. 1548 patients were recruited. The mean blood glucose values differed significantly between groups, 5.7±1.1 mmol/l and 8.5±1.8 mmol/l. Tight glycaemic control resulted in a significant mortality benefit during the ICU stay, 4.6% vs 8.0%; P<0.04), as well as reducing bloodstream infections, acute kidney injury requiring renal replacement therapy, red cell transfusions and critical-illness polyneuropathy. Three aspects of the trial limited external generalisability – namely, the large percentage of cardiac surgical patients, the frequency of parenteral nutrition and its single-centre nature. Despite these concerns, this landmark trial influenced glycaemic control worldwide in a very short space of time.

NICE-SUGAR was a large ANZICS multi-centre randomised controlled trial comparing tight glycaemic control (4.5 to 6.0 mmol/l) with liberal control (<10 mmol/l) in 6,104 critically ill patients expected to stay in the ICU for at least three days. Tight glycaemic control resulted in excessive mortality, 27.5% vs 24.9%; OR, 1.14; 95% CI,⁴ 1.02 to 1.28; P=0.02). Results were similar for both medical and surgical patients. Rates of hypoglycaemia were significantly higher in the tight glycaemic control group (6.8% vs 0.5%; P<0.001), which was felt to have been responsible for the mortality excess.

The ChiP trial examined whether critically ill children should receive tight glycaemic control. 1,369 children in 13 English PICUs were randomised to either tight glycaemic control (4.0 to 7.0 mmol/l) or conventional glycaemic control (<12.0 mol/l).¹² Groups were similar at baseline. 60% had undergone cardiac surgery and almost two-thirds were aged < 1 year. The tight glycaemic control patients received more insulin and had a lower blood glucose value. There was no difference in the primary outcome of number of days alive and free from mechanical ventilation at day 30 (tight glycaemic control group, 23±0.3 days vs conventional group, 23.2±0.3 days; mean difference 0.36; 95% CI, -0.42 to



1.14). Tight glycaemic control resulted in more children suffering hypoglycaemia (7.3% vs. 1.5%; $P < 0.001$).

Vlasselaers and colleagues also examined the question of intensive insulin therapy for paediatric patients in a randomised controlled trial in 700 critically ill children in Leuven, Belgium.¹³ Patients in the intensive insulin arm had a target blood glucose concentrations of 2.8 to 4.4 mmol/L in infants and 3.9 to 5.6 mmol/L in older children, while the control group was managed with a blood glucose below 12.0 mmol/L. Intensive insulin therapy resulted in a shorter stay in PICU (5.5 days vs 6.2 days; $P = 0.017$), less inflammation, as measured with CRP (-9.75 mg/L vs 8.97 mg/L; $P = 0.007$) and mortality (3% vs 6%; $P = 0.038$). More patients in the intensive insulin group suffered episodes of hypoglycaemia (25% vs 1%).

Should we routinely use early supplementary parenteral nutrition in children at risk for malnutrition and able to receive some enteral feeding?

Probably not. It is unclear that full calorific feeding is either necessary or desirable in the very early stages of critical illness, either in children or adults.

References

1. Prasad V, Vandross A, Toomey C, et al. A Decade of Reversal: An Analysis of 146 Contradicted Medical Practices. *Mayo Clin Proc* 88(8):790–8.
2. Preiser J-C, van Zanten AR, Berger MM, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. *Crit Care* 2015;19(1):35.
3. Fivez T, Kerklaan D, Verbruggen S, et al. Impact of withholding early parenteral nutrition completing enteral nutrition in pediatric critically ill patients (PEPaNIC trial): study protocol for a randomized controlled trial. *Trials* 2015;16(1):202.
4. Investigators TN-SS. Intensive versus Conventional Glucose Control in Critically Ill Patients. *N Engl J Med* 2009;360(13):1283–97.
5. Van den Berghe G, Wouters P, Weekers F, et al. Intensive Insulin Therapy in Critically Ill Patients. *N Engl J Med* 2001;345(19):1359–67.
6. Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. *Jama* 2013;309(20):2130–8.
7. Casaer MP, Mesotten D, Hermans G, et al. Early versus Late Parenteral Nutrition in Critically Ill Adults. *N Engl J Med* 2011;365:506-17



8. Hermans G, Casaer MP, Clerckx B, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. *Lancet Respir Med* 1(8):621–9.
9. Heidegger CP, Berger MM, Graf S, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *The Lancet* 2013;381(9864):385–93.
10. The National Heart and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Initial Trophic vs Full Enteral Feeding in Patients With Acute Lung Injury: The EDEN Randomized Trial. *JAMA J Am Med Assoc* 2012;307(8):795–803.
11. Mehta. Parenteral Nutrition in Critically Ill Children. *N Engl J Med* 2016;374:1190-1192
12. Macrae D, Grieve R, Allen E, Sadique Z, Morris K, Pappachan J, et al. A Randomized Trial of Hyperglycemic Control in Pediatric Intensive Care. *N Engl J Med* 2014;370:107-18
13. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. *Lancet* 2009;373(9663):547-56



POP-UP

Selvanderan SP, Summers MJ, Finis ME, Plummer MP, Abdelhamid YA, Anderson MB et al. Pantoprazole or Placebo for Stress Ulcer Prophylaxis (POP-UP): randomised Double-Blind Exploratory Study Crit Care Med 2016; 44(10):1842-1850

Introduction

Clinical practice guidelines recommend gastric acid suppressive agents for prophylaxis against stress ulceration in mechanically ventilated patients.¹ As a means to achieving gastric acid suppression, proton pump inhibitors (PPIs) are ubiquitous within the ICU environment. The evidence base for stress ulcer prophylaxis (SUP) is based largely on trials from over 2 decades ago when processes of care in ICU were very different.² More recent evidence suggests the incidence of stress ulceration in ICU patients is very low at approximately 1%.³

ICU-acquired infections such as *Clostridium difficile* and ventilator-associated pneumonia (VAP) have been associated with the use of PPIs.^{3,4} Although there was a vogue for including PPIs as part of a “ventilator care bundle,” recent guidelines definitively advise against their use to prevent VAP, suggesting that in patients who receive a combination of enteral nutrition and PPI, the rates of VAP and mortality may actually be increased.⁵ With an unconvincing evidence-base and the potential for harm, the therapeutic role of PPIs in the modern day ICU, where early enteral nutrition is the norm, is now uncertain. This trial sought evidence of benefit or harm, associated with the use PPIs in an Australian university-affiliated quaternary ICU within which the provision of PPIs for mechanically ventilated patients and early enteral nutrition were the standard of care.

Study synopsis

POP-UP was a single-centre randomised, double-blind, placebo-controlled, parallel group trial carried out in a mixed medical-surgical ICU. Eligible patients were randomised to receive a once daily dose of either 40mg of pantoprazole in 10ml of 0.9% saline or placebo (10ml of 0.9% saline). All patients admitted to the ICU who were expected to be mechanically ventilated for more than 24 hours and who were expected to commence on enteral feeding within 48 hours were eligible for inclusion. Non-intubated patients were excluded. Patients who were prescribed acid suppressive therapy prior to admission, those admitted with GI bleed, known peptic ulcer disease or prescribed a steroid dose equivalent to greater than 100 mg prednisolone per day were also excluded.

A power calculation was not carried out. As an exploratory study, every admission was assessed and all eligible patients at this institution were enrolled over a 12 month



period. It was hoped the event rate data generated would then inform the design of a larger future phase III study. Analysis was based on the intention-to-treat model.

The hospital pharmacy prepared the study packs and randomised eligible patients in a 1:1 ratio. All medical, nursing and research staff were blinded to group allocation. Patients received the intervention or control until extubation or for up to 14 days post randomisation. The three primary outcome measures were clinically significant gastrointestinal (GI) bleeding, incidence of ventilator-associated infection or pneumonia and incidence of *Clostridium difficile* infection.

Clinically significant GI bleeding was defined as an overt episode of bleeding accompanied within 24 hours by a drop in MAP \geq 20mm Hg or a drop in Hb \geq 20 g/L in the absence of another cause. The need for endoscopy or surgery to arrest the bleeding also fulfilled the definition. VAP was defined according to the CDC definitions. A clear protocol was in place for stool sampling and testing for *Clostridium difficile*.

Secondary outcome measures included the rate of overt GI bleeding, daily Hb concentration, transfusion of red cells, time to first dose and number of doses of study drug received and ventilator-free days at day 28. Coagulation and platelet counts were recorded at enrolment to categorise the presence of haemostatic dysfunction and data was also collected on enteral nutrition during the study.

Of 1,632 patients admitted during the study period, 216 (13%) were randomised. 978 (60%) patients were excluded as they were not intubated or expected to extubate in less than 24 hours. Of 645 patients expected to be mechanically ventilated for more than 24 hours, the most common reasons for exclusion were existing acid suppressive therapy, steroid therapy, known peptic ulcer disease or active GI bleed. Consent was withdrawn for 2 patients, so 214 were included in the intention-to-treat analysis – 106 in the treatment arm and 108 in the control arm. Two patients were lost to follow-up in the treatment arm and 3 patients in the control arm.

Groups were well matched at baseline, with an average age of 52, and two-thirds were male. Approximately 50% in each group were on inotrope/vasopressor infusion. More patients in the placebo group were immunosuppressed (18.5% vs 5.6%). 69% of patients included in the study were of a non-operative primary diagnostic group, with 31% admitted to ICU post-operatively. Groups were balanced in terms of post-operative vs non-operative admissions.

Both groups received a median number of 3 doses of study drug. The first dose was administered within a median of 16 (15-18) vs 17 (16-19) (P=0.44) hours in the treatment and control groups, respectively. Over 80% of patients in each group received enteral nutrition within a median time of 16 hours of initiation of mechanical ventilation.



Volume of feed delivered and incidence of feed intolerance was well matched between groups. There were no significant differences between groups in the use of corticosteroids, antibiotics or inotropes/vasopressors during the study period. The incidence of haemostatic dysfunction was similar between groups, 37% vs 32%, in treatment vs control groups, respectively.

There were no recorded episodes of clinically significant GI bleeding in either group. Ventilator-associated infective complications or pneumonia occurred in 1.9% (95% CI, 0.2 to 5.1) and 0.9% (95% CI, 0.02 to 5.2), and *Clostridium difficile* infection occurred in 1/106 vs 0/108 in the treatment and control arms, respectively. Nine patients had clinically overt GI bleeding during the study period 3/106 (2.8%; 95% CI 0.6-8.0) vs 6/108 (5.6%; 95% CI 2.1-11.7) (P=0.5). In eight of these cases the study drug was switched to open-label pantoprazole but no other intervention was required.

When adjusted for transfusion, daily haemoglobin concentrations did not differ significantly between groups. Rate of red cell transfusion did not differ, nor was any significant difference between groups detected in ventilator-free days, length of ICU or hospital stay or 90 day mortality.

Study critique

This study recruited mechanically ventilated patients at low risk of stress ulceration and found no evidence of benefit or excess harm associated with the use of PPIs. As this was an exploratory trial a power calculation was not carried out and all eligible patients were enrolled over a 12 month period. Thus, it was underpowered to detect clinically important outcomes. Both interventions were considered standard-of-care in this ICU. Almost all randomised patients received study drug and 98% completed follow-up which is reassuring when planning for a large phase III trial.

Patients received the first dose of study drug in a timely fashion, but a mean number of just three doses were given in each group. With a mean of 21 ventilator-free days in each group perhaps patients were not intubated for long enough to expose them to significant risk of either GI haemorrhage or VAP. Furthermore, the ability of just a few doses of PPI to influence the development *Clostridium difficile* infection is uncertain.

Patients randomised in this trial were commenced on enteral nutrition within 24 hours in 85% of cases. The early implementation of enteral nutrition may itself have reduced the rate of stress ulceration by exerting a protective influence on gastric mucosa and thereby offsetting any potential benefits of PPI. Although numbers were small (n=9), mechanically ventilated patients who were not expected to be enterally fed within 48 hours of admission were excluded.

Only 13% of patients assessed for enrolment into the trial were randomised. This may



have been as the investigators wished to generate data for the risk/benefit profile of PPIs in a low risk population. Many patients were excluded because they were not intubated or expected to be extubated within 24 hours. A significant proportion were also excluded as they were already receiving or had been exposed to PPIs prior to admission.

An interesting observational data set, separate from the randomised controlled trial, may have been to monitor and publish the prescription of PPIs, the rate of ventilator-associated infective complications, GI bleeding and *Clostridium difficile* infection among those patients in the ICU but excluded from the actual RCT. Although observational, this data may have provided additional information on association and may have been more representative of care processes within the ICU in question.

Where this sits in the body of evidence

The association of PPI use and development of *Clostridium difficile* infection was studied in a single-centre retrospective analysis of data from 3,286 medical ICU patients in Germany.⁴ 73% of patients received a PPI during the ICU stay. The rate of GI bleeding was low at 0.9%. Univariate analysis showed PPI use was associated with a higher risk of developing *Clostridium difficile*, OR 3.5, 95% CI; 1.87 to 6.55). This was confirmed on multivariate regression, OR 3.11; 95% CI; 1.11 to 8.74).

Marik published a meta-analysis of randomised controlled trials comparing histamine receptor antagonists (H2RA) vs placebo for stress ulcer prophylaxis in ICU patients.³ The primary endpoint was the incidence of significant GI bleed. Secondary endpoints were hospital-acquired pneumonia (HAP) and hospital mortality. 17 studies were included. Only 3 studies, however, included patients with an adequate rate of enteral nutrition. Stress ulcer prophylaxis with H2RA reduced the rate of clinically significant GI bleeding. (OR, 0.47; 95% CI, 0.29 to 0.36; P<0.002). The benefit in reduction of GI bleeding was confined solely to those patients who were not enterally fed. If patients were enterally fed and received stress ulcer prophylaxis, there was no reduction in GI bleeding but an association with increased risk of HAP (OR, 2.81; 95% CI, 1.2 to 6.56, P=0.02) and mortality (OR, 1.89; 95% CI, 1.04 to 3.44; P=0.04).

In an effort to describe the current use of acid suppressants and to ascertain the prevalence of risk factors for, and prognostic significance of, GI haemorrhage, Krag et al performed an international multi-centre inception cohort study over a 7 day period between December 2013 and April 2014.⁶ 97 ICUs in 11 countries contributed to data collection from 1,034 patients. 73% of patients were prescribed a gastric acid suppressant with 573/1034 (55%) receiving a proton pump inhibitor. Clinically significant GI bleeding occurred in 2.6% (95% CI 1.6 to 3.6) of cases. After co-variate adjustment, clinically significant GI bleeding did not impact the risk of 90-day mortality. This study did not collect data on harm associated with use of PPIs.



Another meta-analysis involving 14 trials and 1,720 patients compared PPIs with H2RA in stress ulcer prophylaxis.⁷ Primary outcome measures were clinically important and overt upper GI bleeding. Pneumonia and *Clostridium difficile* infection were included as secondary outcomes. No trials in this meta-analysis provided direct data on the influence of enteral nutrition on GI bleeding. PPIs did reduce the rate of clinically significant GI bleed vs H2RA (RR 0.36; 95% CI, 0.19 to 0.68; P=0.002). PPIs also reduced the rate of overt GI bleed (RR, 0.35; 95% CI, 0.21 to 0.59; P<0.0001). No difference between PPIs vs H2RA in nosocomial pneumonia, ICU mortality or ICU length of stay was detected. The sparsity of data, mixed quality of the included trials and possible risk of publication bias are all acknowledged in this meta-analysis.

In a retrospective pharmaco-epidemiological cohort study, data from 35,312 ICU patients mechanically ventilated for over 24 hours, and who received either a H2RA or a PPI for 48 hours or more, was analysed.⁸ Primary outcomes were rates of GI bleeding, pneumonia and *Clostridium difficile* infection coded as secondary diagnoses as per the ICD-9. 38.1% of patients in this databank received a H2RA and 61.9% a PPI. Rates of GI bleed (2.1% v 5.9%; P<0.001), pneumonia (27% v 38.6%; P<0.001) and *Clostridium difficile* (2.2% v 3.8%; P<0.001) were lower in the H2RA group compared to PPIs.

Twenty randomised controlled trials involving 1,971 patients were included in another meta-analysis of stress ulcer prophylaxis vs placebo or no prophylaxis.⁹ Primary outcome measures included rate of GI bleed, HAP and all-cause mortality. There was considerable heterogeneity among included trials. The quality of evidence from these trials was low, with a high risk of bias. No difference in mortality, GI bleeding or HAP was detected between stress ulcer prophylaxis vs placebo or no prophylaxis.

A retrospective cohort study extracted data from a large Japanese database on stress ulcer prophylaxis in patients admitted with severe sepsis.¹⁰ Data was retrieved on over 70,000 patients from 526 hospitals. Propensity scores were used to create treatment (stress ulcer prophylaxis) and control groups (placebo or no prophylaxis) which were well balanced and included 15, 651 patients in each group. No difference in the rate of GI bleeding requiring endoscopic intervention, *Clostridium difficile* or 30 day mortality was detected. A higher rate of HAP was detected in the SUP group (3.9% v 3.3%) P = 0.012.

We look forward to the results of large phase III studies currently progressing, which will further enhance our understanding of this area.^{11,12}

Should we implement this into our practice?

No. We should not change practice on the basis of this exploratory single-centred trial. We must, however, question the role of PPIs in modern day stress ulcer prophylaxis.



References

1. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39(2):165–228.
2. Marik PE. Stress Ulcer Prophylaxis Deadoption: What is the Barrier? *Crit Care Med* 2016;44(10):1939–1941.
3. Marik PE, Vasu T, Hirani A, Pachinburavan M, et al. Stress ulcer prophylaxis in the new millennium: a systematic review and meta-analysis. *Crit Care Med* 2010;38(11):2222–2228.
4. Buendgens L, Bruensing J, Matthes M, et al. Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing *Clostridium difficile*-associated diarrhea. *J Crit Care* 2014;29(4):e11-5
5. Klompas M, Branson R, Eichenwald EC, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol* 2014;35(S2):S133–54.
6. Krag M, Perner A, Wetterslev J, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med* 2015;41(5):833–845.
7. Alhazzani W, Alenezi F, Jaeschke RZ, Moayyedi P, Cook DJ. Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis. *Crit Care Med* 2013;41(3):693–705.
8. MacLaren R, Reynolds PM, Allen RR. Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the ICU. *JAMA Intern Med* 2014;174(4):564–574.
9. Krag M, Perner A, Wetterslev J, Wise MP, Møller MH. Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. *Intensive Care Med* 2014;40(1):11–22.
10. Sasabuchi Y, Matsui H, Lefor AK, Fushimi K, Yasunaga H. Risks and Benefits of Stress Ulcer Prophylaxis for Patients With Severe Sepsis. *Crit Care Med* [Internet] 2016 [cited 2016 Oct 25]; Available from: <http://europepmc.org/abstract/med/27002276>
11. Krag M, Perner A, Wetterslev J, et al. Stress ulcer prophylaxis with a proton pump inhibitor versus placebo in critically ill patients (SUP-ICU trial): study protocol for a randomised controlled trial. *Trials* 2016;17(1):205
12. Re-Evaluating the Inhibition of Stress Erosions: Gastrointestinal Bleeding Prophylaxis In ICU - Full Text View - ClinicalTrials.gov [Internet]. [cited 2016 Oct 26]; Available from: <https://clinicaltrials.gov/ct2/show/NCT02290327>



Renal Trials



AKIKI

Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. *N Eng J Med* 2016;375:122-133

Introduction

Much of the research in renal replacement therapy (RRT) in critical illness has focused on the effect of dose on outcome.^{1,2} However, in the absence of life-threatening complications, there is no consensus on the timing of initiation of RRT in acute kidney injury (AKI).³ There are multiple, theoretical benefits to early RRT in relation to fluid balance and metabolic control; indeed, observational studies have suggested early initiation is beneficial.⁴ In contrast, in a cohort of septic patients, initiation of RRT prior to the development of renal failure has shown to be potentially detrimental.⁵ The Artificial Kidney Initiation in Kidney Injury (AKIKI) trial investigated the timing of initiation of RRT in critically ill patients with established renal injury.

Study synopsis

This multi-centre, randomised controlled trial performed in 31 French ICUs investigated the effect of an early versus a delayed strategy for the initiation of RRT. Adult patients admitted to ICU who fulfilled criteria for KDIGO stage 3 AKI and required vasopressor support, mechanical ventilation or both were eligible.⁶ Patients fulfil KDIGO stage 3 if they meet any one of the following criteria; serum creatinine 3 times baseline, serum creatinine $\geq 354 \mu\text{mol/L}$, urine output $< 0.3 \text{ ml/kg}$ for > 24 hours or anuria for ≥ 12 hours. Patients were excluded if they met criteria for immediate dialysis: uraemia (blood urea nitrogen (BUN) $> 40 \text{ mmol/L}$), hyperkalaemia (potassium $> 6 \text{ mmol/L}$ or $> 5.5 \text{ mmol/L}$ after medical treatment), metabolic acidosis ($\text{pH} < 7.15$) or diuretic-resistant pulmonary oedema.

The early strategy group had RRT commenced within six hours of meeting the inclusion criteria. The late strategy group only had RRT commenced if they met the criteria for immediate dialysis (stated above) or were oliguric for 72 hours after randomisation. There was no blinding of treatment allocation. The method and duration of RRT were at the discretion of the treating clinicians. Discontinuation of RRT was recommended when urine output was $> 1 \text{ L/day}$ (or 2 L/day with diuretics) and mandated when creatinine fell due to spontaneous diuresis.

The primary outcome measure was survival 60 days after randomisation. Secondary endpoints included the requirement for RRT, time from randomisation to initiation of RRT, number of RRT sessions required, RRT dependence at days 28 and 60, days free from a variety of organ support measures, dialysis catheter free days, SOFA scores on day three and seven, hospital and intensive care length of stay, nosocomial infections



and predefined complications related to RRT.

Assuming an estimated 60-day mortality of 55% in ICU patients requiring RRT, a total sample size of 546 patients was calculated to have 90% power at the 5% significance level, to detect an absolute difference in mortality of 15% in favour of a delayed treatment strategy. After taking into account the planned interim analysis, and to allow for loss to follow-up, a sample size of 620 patients was required.

In total 5,528 patients with AKI who were ventilator-dependant, inotrope-dependant or both were screened. 3,430 fulfilled KDIGO stage 3 criteria; 2,583 of these met exclusion criteria, and 227 eligible patients were missed. Ultimately a total of 620 patients were randomised; 312 to the early strategy group and 308 to the delayed strategy group. Baseline characteristics were similar in the two groups; 86% of patients were mechanically ventilated and 85% required vasopressor support. The majority of patients (80%) had a diagnosis of sepsis. The mean SOFA score was 10.9 ± 3.2 vs 10.8 ± 3.1 in the early and delayed strategy groups, respectively.

In the early strategy group, RRT was commenced within a median of 2 hours after randomisation and 4.3 hours after meeting KDIGO stage III criteria. 99% of this group received RRT. In the delayed strategy group, 51% received RRT at a median time of 57 hours after randomisation. In this group, uraemia (38%) and oliguria/anuria at 72 hours (38%) were the commonest reasons for dialysis. For those who required RRT in the delayed strategy group, the median urine output in the 24 hours prior to RRT was 150 ml (IQR 50 to 600). RRT was initiated at a creatinine of 289 $\mu\text{mol/L}$ vs 471 $\mu\text{mol/L}$ in the early and delayed strategy groups, respectively. Intermittent hemodialysis was the initial method of RRT in 55% of patients.

There was no difference in the primary outcome measure of 60-day mortality; 48.5% (95% CI, 42.6 to 53.8) vs 49.7% (95% CI, 43.8 to 55.0) in the early and delayed strategy groups, respectively (hazard ratio, 1.03; 95% CI, 0.82 to 1.29; $P=0.79$). A post hoc exploratory analysis demonstrated mortality was lowest in the cohort of patients who did not require RRT in the delayed strategy group (37.1%). However, after adjustment for baseline Simplified Acute Physiology Score III, the difference in mortality between this subgroup and those in the early strategy group was not statistically significant ($P=0.341$). Similarly, there was no difference in mortality for those who did require RRT in the delayed strategy group (61.8%) and the early strategy group ($P = 0.181$).

The delayed strategy group had significantly more days free from RRT at day 28, 19 (IQR 5 to 29) vs 17 (IQR 2 to 26), ($P<0.001$). The overall number of RRT sessions was lower in the delayed strategy group (943 vs 1,665). The early treatment group had more episodes



of hypophosphataemia (22% vs 15% $P=0.03$) and more catheter-related blood stream infections (10% vs 5%; $P=0.03$). It is notable that 55% of dialysis lines were in the femoral vein. There were no significant differences in any other pre-specified secondary outcomes.

Study critique

AKIKI is currently the largest multi-centre trial investigating the timing of renal replacement therapy in the critically ill. It has numerous praiseworthy features. In initiating RRT just 4.3 hours after KDIGO stage 3 was reached in the early strategy group, it achieved excellent separation between the two groups. The late initiation of RRT in the delayed strategy group appeared safe; although it resulted in higher rates of hyperkalaemia and acidosis requiring treatment (both $P<0.001$), there was no evidence of serious harm. In interpreting the results of this trial, the selective nature of the patient cohort must be borne in mind; just 11% of the patients screened were included and more patients were excluded due to a need for immediate RRT ($n = 663$) than were ultimately enrolled in the trial.

The hypothesis of the trial was that a delayed strategy would translate into a reduced mortality; this is an unusual concept for critical illness. The investigators argue a delayed strategy would allow for stabilisation before initiation of RRT or avoidance altogether. RRT can cause loss of amino acids, vitamins, catecholamines and electrolytes (particularly phosphate which may result in respiratory and cardiac dysfunction).⁷⁻⁹ This must be balanced against the acidosis, hyperkalaemia and pulmonary oedema seen when initiation of RRT is delayed. Overall, it is difficult to envisage that avoidance of RRT in a small cohort of patients could lead to a 15% absolute reduction in mortality. Almost half of the delayed strategy group did avoid the intervention and any associated complications.

In contrast to the ELAIN study, which enrolled patients at KDIGO stage 2, this trial recruited patients with KDIGO stage 3.^{6,10} Arguably increases in urea and creatinine are late signs of renal damage. The creatinine levels at which RRT was initiated (289 vs 471 $\mu\text{mol/L}$ in the early and delayed strategy groups, respectively) suggest that this was ultimately a trial of late compared to even later initiation of RRT.

Again, in contrast to the ELAIN study, neither the dose nor method of RRT was standardised.¹⁰ Intermittent haemodialysis was the initial method of RRT in 55% of patients, with just 30% receiving continuous RRT (CRRT) as their sole method of dialysis. This does not reflect UK, or many other countries, practice, where CRRT is preferred.¹¹ There is conflicting evidence as to the optimal mode of RRT in critically ill patients. Several small randomised trials have failed to show any differences in mortality or renal outcomes.¹²⁻¹⁴ However in two large trials investigating RRT dosing in critically ill patients, the renal outcomes were significantly better in the trial which used CRRT.^{1,2} A



meta-analysis and further observational data support this finding.^{15,16}

Failure to standardise the dose of RRT delivered may have introduced a confounding variable. As no data is presented on dialysis dose per se, we must rely on surrogates. The authors state the urea levels during RRT reflect adequate dosing (early strategy 13.5 mmol/L vs delayed 20.3 mmol/L). However, the urea observed during RRT in the delayed strategy group is considerably higher than that seen in the trials which looked at dialysis dose. In the RENAL trial, for example, RRT was commenced at a urea 22.8 mmol/L in the low intensity group and fell to 15.9 mmol/L.² This is in contrast to a urea of 32 ± 12 mmol/L prior to RRT in the delayed strategy group. Therefore, direct comparisons are difficult to make and little inference can be drawn about the dialysis dose delivered and whether it was adequate in either group.

One potential advantage of early RRT is the control of fluid balance. Excessive positive fluid balance has been shown to be detrimental in lung injury and in critically ill patients with renal injury.¹⁷⁻²⁰ Although information is provided on diuresis, no data is provided on fluid balance. The delayed strategy group received more diuretics prior to RRT but without fluid balance the effects of such interventions are not known. This is disappointing as the urine outputs were closely monitored.

Furthermore, a urine output of $> 1,000$ mls/day (in the absence of diuretics) was used as a measure of return of renal function. Using this cut off, the delayed strategy group had faster return of renal function. However, although urine output is associated with return of renal function, a more conservative urine output might have been more sensitive.^{21,22}

In summary, whilst trials examining RRT dose have been criticised for not standardising when dialysis was initiated, the AKIKI trial could equally be criticised for failing to standardise dose and method of RRT. The absence of data on dialysis dose and fluid balance is a limitation. Unsurprisingly, in the delayed RRT group only the most severely ill patients went on to require RRT. In contrast, some patients in the early strategy group may have been dialysed unnecessarily. Future work should concentrate on better identifying which patients are likely to go on to require RRT.

Where this sits in the body of evidence

The ELAIN trial was a single-centre study involving 231 critically ill patients with KDIGO AKI stage 2 (creatinine > 2 times baseline or urinary output < 0.5 mL/kg/h for >12 hours) and a plasma NGAL level > 150 ng/mL. Patients were randomised to early RRT (commenced within 8 hours of KDIGO stage 2) or delayed RRT (commenced within 12 hours of KDIGO stage 3). All 112 patients in the early group and 108 / 119 patients in the delayed group underwent RRT. The median time to initiation was 6 hours for the early group and 25.5 hours for the delayed group. 90 day mortality was 39.3% in the early group compared with 54.7% in the delayed group, (absolute risk reduction, -15.4%; 95%

CI, -28.1% to -2.6%; P=0.03). The early group also had a shorter median duration of RRT (9 days vs 25 days), shorter duration of mechanical ventilation (125.5 hrs vs 181 hrs), and shorter hospital length of stay (51 days vs 82 days). Recovery of kidney function without the need for dialysis was also more common in the early RRT group (53.6% vs 38.7%).¹⁰

In an observational study over 8 years in a level one trauma centre, 100 adult trauma patients treated with RRT were characterized as "early" or "late" starters, based upon whether the urea was less than or greater than 21 mmol/L, prior to CRRT initiation. The mean urea in the early and late group was 15.2 vs 33.7 mmol/L, respectively (P < 0.0001). Survival was significantly higher among early starters compared to late starters (39.0% vs 20.0%, respectively; P = 0.041).²³

In a prospective, multi-centre, observational study conducted in 54 ICUs in 23 countries, 1,238 patients who received RRT were stratified into "early" and "late" starters based on urea, creatinine or time from ICU admission. There was no difference in crude or covariate-adjusted mortality between those who commenced RRT at a urea of < 24 mmol/L vs > 24 mmol/L. When stratified by creatinine, late RRT (commence at creatinine > 309 µmol/L) was associated with lower crude and covariate-adjusted mortality. However, RRT commenced > 5 days after ICU admission was associated with greater crude and covariate-adjusted mortality.⁴

In a small multi-centre observational study, 98 patients who required RRT after abdominal surgery according to local indications were divided into early dialysis (sRIFLE-0 or Risk) and late dialysis (sRIFLE -Injury or Failure) groups. The overall mortality was 58.2%. Late dialysis was an independent risk factor for in-hospital mortality (hazard ratio, 1.846; P = 0.027).²⁴

A substudy of the Finnish Acute Kidney Injury study looked at 2,901 patients with AKI. The 239 patients who required RRT were classified as classic (one or more conventional indications, n=134) and pre-emptive (no conventional indications, n=105). Crude 90-day mortality was 48.5% vs 29.5% for the classic and pre-emptive groups, respectively. Classic RRT was associated with a higher risk for mortality (adjusted odds ratio, 2.05; 95% CI, 1.03 to 4.09).²⁵

In a randomised, controlled trial, 106 ventilated patients were allocated to early high-volume haemofiltration (72 - 96 L per 24 hrs), early low-volume haemofiltration (24 - 36 L per 24 hrs), or late low-volume haemofiltration (24 - 36 L per 24 hrs). Early initiation was within 12 hours of oliguria (< 30 ml/h for six hours) and a creatinine clearance < 20 mls/min. Late initiation was after the development of a traditional indication for RRT. There was no difference in survival at day 28 or renal recovery in any of the groups.²⁶



Should we routinely start early renal replacement therapy in those with acute kidney injury?

Possibly not. The evidence remains unclear and further evidence is needed on the initiation of RRT in critical illness.

References

1. The VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008; 359: 7-20.
2. The RENAL Replacement Therapy Study Investigators. Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients. *N Engl J Med* 2009; 361:1627-1638.
3. Legrand M, Darmon M, Joannidis M & Payen D. Management of renal replacement therapy in ICU patients: an international survey. *Intensive Care Med* 2013; 39: 101-8.
4. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M et al. Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury. *J Crit Care* 2009; 24: 129-40.
5. Payen D, Mateo J, Cavaillon JM, Fraisse F, Floriot C & Vicaut E. Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: a randomised controlled trial. *Crit Care Med* 2009; 37: 803-10.
6. Section 2: AKI definition. *Kidney Int Suppl* (2011) 2012; 2: 19-36.
7. Btaiche IF, Mohammad RA, Alaniz C, Mueller BA. Amino acid requirements in critically ill patients with acute kidney injury treated with continuous renal replacement therapy. *Pharmacotherapy*. 2008;28:600-13.
8. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*. 2009;361:1627-38.
9. Hiremath S, Slivar S & Magner P. Phosphate balance with continuous renal replacement therapy: a simple solution. *Am J Kidney Dis*. 2013;62:644.
10. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H et al. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury. The ELAIN randomised Clinical Trial. *JAMA* 2016;315(20):2190-2199.
11. Gatward JJ, Gibbon GJ, Wrathall G, Padkin A. Renal replacement therapy for acute



- renal failure: a survey of practice in adult intensive care units in the United Kingdom. *Anaesthesia* 2008;63:959-66.
12. Vinsonneau C, Camus C, Combes A, de Beauregard MAC, Klouche K, Boulain T et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multi-centre randomised trial. *Lancet*. 2006;368:379–385.
 13. Lins RL, Elseviers MM, Van der Niepen P, Hoste E, Malbrain ML, Damas P et al. Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomised clinical trial. *Nephrol Dial Transplant*. 2009;24:512–518.
 14. Schefold JC, Haehling S von, Pischowski R, Bender TO, Berkmann C, Briegel S et al. The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): a prospective randomised controlled trial. *Critical Care*. 2014;18(1):R11.
 15. Schneider AG, Bellomo R, Bagshaw SM, Glassford NJ, Lo S, Jun M, et al. Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. *Intensive Care Med*. 2013;39:987–97.
 16. Wald R, Shariff SZ, Adhikari NK, Bagshaw SM, Burns KE, Friedrich JO et al. The association between renal replacement therapy modality and long-term outcomes among critically ill adults with acute kidney injury: a retrospective cohort study. *Crit Care Med*. 2014;42(4):868-77.
 17. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B et al. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564-75.
 18. Sakr Y, Vincent JL, Reinhart K, Groeneveld J, Michalopoulos A, Sprung CL, Sepsis Occurrence in Acutely Ill Patients Investigators et al. High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. *Chest*. 2005;128:3098–108.
 19. Vaara ST, Korhonen A-M, Kaukonen K-M, Nisula S, Inkinen O, Hoppu S, The FINNAKI Study Group et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. *Crit Care*. 2012;16:R197.
 20. RENAL Replacement Therapy Study Investigators. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lee J, et al. An observational study fluid balance and patient outcomes in the randomised evaluation of normal vs augmented level of replacement therapy trial. *Crit Care Med*. 2012;40:1753–60.
 21. Wu VC, Ko WJ, Chang HW, Chen YW, Lin YF, Shiao CC, et al. Risk factors of early



- redialysis after weaning from post-operative acute renal replacement therapy. *Intensive Care Med.* 2008;34:101–8.
22. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, et al. Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multi-centre observational study. *Crit Care Med.* 2009;37:2576–82.
23. Gettings LG, Reynolds HN, Scales T. Outcome in posttraumatic acute renal failure when continuous renal replacement therapy is applied early vs late. *Intensive Care Med.* 1999;25(8):805-813.
24. Shiao CC, Wu VC, Li WY, Lin YF, Hu FC, Young GH et al. Late initiation of renal replacement therapy is associated with worse outcomes in acute kidney injury after major abdominal surgery. *Crit Care* 2009; 13: R171.
25. Vaara ST, Reinikainen M, Wald R, Bagshaw SM, Pettilä V. Timing of RRT based on the presence of conventional indications. *Clin J Am Soc Nephrol* 2014; 9: 1577-85.
26. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF & Kesecioglu J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomised trial. *Crit Care Med.* 2002;30(10):2205-2211.

ELAIN

Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H et al. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury. The ELAIN randomised Clinical Trial. JAMA 2016;315(20):2190-2199

Introduction

Acute kidney injury is common in critical illness. It affects up to 60% of intensive care patients, is associated with a mortality of around 25% and, as the severity of acute kidney injury increases, there is a stepwise increase in mortality.¹ Renal replacement therapy (RRT) is frequently used in the management of acute kidney injury in association with multi-organ failure.² However, our understanding of the complexity of renal replacement in the context of critical illness is lacking. Hence the optimal approach to renal replacement therapy is unclear. One such aspect of the treatment that remains controversial is when to initiate therapy. A recent survey identified a multitude of indications in current practice.³ International guidelines are definitive on initiation in the presence of life-threatening indications, but are less clear when to commence in their absence.⁴

Early initiation may allow better control of fluid balance, acidosis and metabolic derangements. Some observational studies have indeed suggested earlier initiation is associated with better outcomes.⁵⁻⁸ Renal replacement is not without risk and possible complications include haemodynamic instability, metabolic derangements and complications of anticoagulation. Consistent with this, observational data has suggested an increased risk of harm with early interventions.^{9,10} Prior to this year, although there have been some randomised trials investigating early versus delayed initiation of RRT, these trials have used different indications for the initiation of therapy and have lacked power to demonstrate an outcome benefit.¹¹⁻¹³ Subsequently, the larger AKIKI trial, which failed to show an outcome benefit from early initiation, was published.¹⁴ The ELAIN trial uses a different early indication for renal replacement and is therefore another important piece in the RRT puzzle.

Study Synopsis

The ELAIN trial was a single-centre, non-blinded, parallel-group randomised trial conducted in a university hospital in Germany. The aim of the study was to investigate the effect of an early versus delayed strategy for the initiation of RRT in the critically ill with acute kidney injury.



Adult intensive care patients with either severe sepsis, requirement for vasopressor support, refractory pulmonary oedema, or progression of non-renal sequential organ failure score, who fulfilled criteria for KDIGO¹ stage two acute renal injury (>2 times baseline creatinine or urinary output <0.5 mL/kg/h for 12 hours) and had an elevated plasma neutrophil gelatinase-associated lipocalin (NGAL) (>150 ng/mL) were eligible for recruitment. Patients were excluded if they had pre-existing renal failure (GFR <30 ml/min), previous RRT, obstructive renal disease or an intrinsic renal pathology such as glomerulonephritis. Pregnancy, HIV, hepatorenal and neutropenic haematological malignancy patients were also excluded.

Randomisation was performed in a 1:1 ratio using a computerised system with stratification based on cardiovascular SOFA score severity and oliguria. The early intervention group had RRT commenced within eight hours of meeting the inclusion criteria, while the late group had therapy commenced within 12 hours of KDIGO stage 3 renal injury (urine output <0.3 mL/kg/h for ≥24 h and/or >3 fold increase in serum creatinine level compared with baseline or serum creatinine of ≥354 µmol/L with an acute increase of 44 µmol/L). RRT was also commenced in the delayed group for absolute indications defined as severe uraemia, hyperkalaemia with ECG changes, hypermagnesaemia, oliguria (<200 ml for 12 hours), anuria or organ oedema despite diuretics. The intervention was standardised in terms of mode (venovenous hemodiafiltration), replacement fluids, blood flow and anticoagulation. Therapy was discontinued with return of urine output (>400 ml/day or >2,100 ml with diuretics) and a creatinine clearance above 20 ml/min. Alternative therapies were allowed if, after 7 days, renal support was still required.

The primary outcome was mortality 90 days after randomisation. Secondary outcomes included: 28- and 60-day mortality, ICU and hospital length of stay, organ dysfunction, defined using daily SOFA scores, recovery of renal function and ongoing need for renal support and serum inflammatory markers. Based on an expected 90-day mortality rate of 55% in the control group with delayed initiation of RRT, 230 patients in total were required to achieve 80% power at the 5% significance level to detect an 18% reduction in 90-day mortality. Analysis was performed on an intention-to-treat principle.

A total of 604 patients with KDIGO stage 2 renal injury were screened, with 231 patients randomised (112 in the early CRRT versus 119 in the delayed group). The majority of patients excluded either did not meet the additional inclusion criteria (66%) or had treatment limitations (26%). Of the 231 patients randomised the majority were either post cardiac (47%) or abdominal surgery (34%). At randomisation baseline creatinine and urine outputs were similar in the groups but there were some baseline differences;



there were more men in the early group (69.6% vs 57.1%), while the delayed group were older (65.7 vs 68.2 years), had higher rates of diabetes (15.2% vs 23.5%), chronic kidney disease (37.8% vs 44.8%) and cardiac arrhythmias (33.0% vs 44.5%). There was a non-significant difference in baseline NGAL levels (early group 618.5 vs delayed group 490.0 ng/ml). Both groups had significant organ dysfunction as indicated by SOFA (early 15.6 vs delayed 16.0) and APACHE 2 scores (early 30.6 vs delayed 32.7).

All patients in the early group received RRT, while 11 patients in the delayed group did not receive the intervention (6 patients did not progress to stage 3 kidney injury, while 5 patients had protocol violations). The early group received RRT within a median of 6.0 hours (IQR 4.0 to 7.0) from randomisation while the delayed group had therapy after a median of 25.5 hours (IQR 18.8 to 40.3); between-group difference, -21.0 hours; 95% CI, -24.0 to -18.0; $P < 0.001$. In the delayed group 18 patients received the intervention before stage 3 kidney injury due to an absolute indication.

There was a significant difference in the primary outcome with a reduced 90-day mortality in the early group, 44 of 112 patients (39.3%) compared to 65 of 119 patients (54.7%) in the delayed group; 95% CI, 0.45 to 0.97; $P=0.03$. There was no significant difference in mortality at 28 days (30.4% early vs 48% delayed, $P=0.11$) or 60 days (38.4% early vs 50.4% delayed, $P=0.07$). The median duration of RRT was reduced in the early group, 9 days (IQR 4 to 44) vs 25 days (IQR 7 to >90; 95% CI, 0.48 to 1.00; $P=0.04$), as was the median length of mechanical ventilation, 125.5 hours (IQR 41 to 203) vs 181.0 hours (IQR 65 to 413); $P=0.002$. Despite reduced duration of mechanical ventilation and renal support, there was no difference in the median duration of intensive care stay 19 days (IQR 9 to 29) in the early group vs 22 days (IQR 12 to 36) in the delayed group, (95% CI, 0.61 to 1.19; $P = 0.33$). Duration of hospital stay was however reduced in the early intervention group 51 days (IQR 31 to 74) vs 82 days (IQR 67 to >90); (95% CI, 0.22 to 0.52; $P<0.001$). At 90 days, there was no difference in requirements for RRT, 13.4% for the early group vs 15.1% for the delayed group.

Study critique

RRT is a complex intervention with multiple aspects of the therapy that could potentially impact on patient outcomes. One such aspect is timing of therapy; traditionally renal replacement was initiated when complications of renal failure were encountered. However, rather than simply a supportive measure in renal failure, evidence has accumulated that earlier intervention may have a therapeutic benefit, at least in terms of attenuating renal injury and accelerating renal recovery.¹⁵ The premise of the ELAIN trial was these potential benefits could impact on mortality in a surgical population of critically ill patients.

The ELAIN trial was a well conducted trial and is currently one of the largest investigating timing of RRT in critical illness. Despite this, with a modest 231 patients from a single-centre, this trial is susceptible to over estimation of treatment effect and false positive findings.¹⁶ ELAIN demonstrated a statistically significant difference for the primary outcome, suggesting early RRT was beneficial. The power calculation was based on an 18% absolute risk reduction in mortality, which seems improbable for any intervention in critical care. The statistical weakness is further highlighted by the fragility index of just three patients.

The investigators successfully enrolled an adequate number of patients based on the power calculation. The patients recruited were critically unwell surgical patients. There were a large number of exclusions based on the strict recruitment criteria. Patients with previous renal disease or intrinsic renal disease were excluded. Of the 604 patients who did meet renal injury inclusion criteria, a further 373 were excluded mainly due to the absence of sepsis, inotropes or fluid overload. However there were minimal patients who met the inclusion criteria who were not recruited. The study should therefore be interpreted in the context of this highly selected population.

The ELAIN trial enrolled patients at KDIGO stage two renal injury. This may not reflect contemporary critical care where practice³ and current recommendations⁴ would suggest RRT is based on the patient's overall condition. In the context of a trial, the KDIGO definitions are validated markers of risk. Initially the use of KDIGO definitions seems a robust comparable measure of renal function. Yet using creatinine and urinary output may raise some issues. Both urea and creatinine are surrogate measures for glomerular filtration rate and are affected by multiple patient related factors, while urinary output not only reflects renal function but also fluid status and is highly influenced by diuretic use in the critically ill patient. Perhaps creatinine clearance might have been a more comparable measure of renal injury. Furthermore, substantial kidney injury may occur before elevations in serum creatinine. In this study, the early intervention group had a median creatinine of 168 $\mu\text{mol/L}$ and urea of 13.7 mmol/L , indicating that the intervention was certainly initiated early in the context of therapy for life threatening complications of renal failure. Arguably in terms of nephron damage this may already reflect substantial damage, a truly early intervention may require a different measure of renal injury. The trial did incorporate a biomarker, NGAL in the inclusion criteria. All patients had to have a serum NGAL $>150 \text{ ng/mL}$, levels above which have been identified as a good indicator for subsequent requirement for RRT.¹⁷ NGAL exists in different molecular forms, is synthesised in bone marrow and stored in neutrophils. Expression also occurs in several non-haematopoietic tissues, such as colon, trachea, lung and kidney epithelium.¹⁸ As plasma NGAL levels are affected by chronic



renal disease and critical illness, the value of NGAL in predicting renal injury has been questioned.¹⁹ In this trial NGAL was used to ensure recruited patients would subsequently require renal replacement and therefore avoid unnecessary interventions. As only three patients were excluded on the basis of the NGAL results it is questionable if this added value to the overall study. Furthermore the control group received renal support at KDIGO stage three renal injury, the same stage as the intervention group in the AKIKI trial, a trial in which 49% of patients did not subsequently require RRT.

The intervention in the ELAIN trial was continuous venovenous hemodiafiltration. Pre-filter replacement fluid was delivered with a ratio of 1:1 with dialysate. The effluent flow prescribed at 30 ml/kg/hr and citrate used for anti-coagulation. Delivery was monitored and strictly adhered to in both groups. There was less than 24 hours between commencing the intervention in the two groups. At initiation, there were significant differences in the serum urea (13.7 vs 16.9 mmol/L), creatinine (168 vs 212 µmol/L) and urine output (445 vs 270 ml) but the potassium and bicarbonate levels were similar. Fluid balance was not different in the two groups. In the context of critical illness it is hard to imagine how these modest clinical differences and delay of around 21 hours in therapy resulted in such a dramatic effect on mortality. It is further perplexing that the intervention effect only became apparent after 90 days, as mortality up to that point was not significantly different. The investigators postulate that reduced inflammatory mediators may have been responsible for the reduction in mortality. Indeed, some pro-inflammatory mediators (IL-6, IL-8) were significantly reduced. However, there was no difference in several other pro-inflammatory mediators. Although a reduction in potentially damaging inflammation seems like a plausible explanation, this may not be supported by current evidence. Firstly, inflammatory mediators vary widely in patients with sepsis,²⁰ and secondly, standard filtration or dialysis membranes have only limited effectiveness in removing cytokines.²¹ Finally, increased dose of therapy should perhaps impact on outcomes. While one large trial²² in septic patients did show a benefit of increased dose, two large trials did not.^{23,24} These studies used more traditional initiation criteria and hence it may be a case of timing. Perhaps if early initiation is important, as this trial suggests, then dosing will also have to be re-examined.

Where this sits in the body of evidence

Although the majority of large renal replacement trials have focused on dose rather than initiation of therapy, there are some trials looking at this important aspect of RRT.

In an observational study over 8 years in a level one trauma centre, 100 adult trauma patients treated with RRT were characterized as "early" or "late" starters, based upon whether the blood urea nitrogen (BUN) was less than or greater than 21 mmol/L, prior to



CRRT initiation. The mean urea of the early and delayed group was 15.2 and 33.7 mmol/L, respectively ($P < 0.0001$). Survival rate was significantly increased among early starters compared to late starters (39.0 vs 20.0 %, respectively, $P = 0.041$).²⁵

In a prospective multi-centre observational study conducted at 54 intensive care units in 23 countries, 1,238 patients were stratified into "early" and "late" by median urea and creatinine levels. Timing was also categorized into early (<2 days), delayed (2 to 5 days), and late (>5 days). RRT by serum urea (<24mmol vs >24mmol) showed no significant difference in crude or covariate-adjusted mortality. When stratified by creatinine (<309 umol/L vs >309 umol/L), late RRT was associated with lower crude and covariate-adjusted mortality. For timing relative to ICU admission, late RRT was associated with greater crude and covariate-adjusted mortality.⁵

In a small multi-centre, observational study 98 patients after abdominal surgery who required RRT according to local indications were divided into early dialysis (sRIFLE-0 or Risk) and late dialysis (LD, sRIFLE -Injury or Failure) groups. Fifty-seven patients (58.2%) died. Late dialysis (HR, 1.846; $P = 0.027$) was an independent risk factor for in-hospital mortality.⁶

In a prospective observational study with 234 patients, RRT was initiated 1 day (0 to 4) after ICU admission. Median creatinine was 331 $\mu\text{mol/L}$ (IQR 225 to 446 $\mu\text{mol/L}$), urea 22.9 mmol/L (13.9 to 32.9 mmol/L), and 76.9% of patients were classed as having RIFLE-Failure acute kidney injury. In adjusted analysis, mortality at renal replacement initiation was associated with creatinine <332 $\mu\text{mol/L}$ (OR, 2.8; 95% CI, 1.5 to 5.4), change in urea from admission >8.9 mmol/L (OR, 1.8; 95% CI, 1.0 to 3.4), urine output <82 mL/24 hours (OR 3.0; 95% CI, 1.4 to 6.5), fluid balance >3.0 L/24 hours (OR 2.3; 95% CI, 1.2 to 4.5), percentage of fluid overload >5% (OR 2.3; 95% CI, 1.2 to 4.7), 3 or more failing organs (OR 4.5; 95% CI, 1.2 to 4.2), Sequential Organ Failure Assessment score >14 (OR 2.3; 95% CI, 1.3 to 4.3), and start 4 days or more after admission (OR 4.3; 95% CI, 1.9 to 9.5). Mortality was higher as factors accumulated.⁷

In a substudy of the Finnish Acute Kidney Injury study, 2,901 patients, patients were classified as pre-emptive (no conventional indications) and classic (one or more indications) RRT recipients. Of 239 patients treated with RRT, 134 fulfilled at least one conventional indication. Crude 90-day mortality of 134 patients with classic indications was 48.5% versus 29.5% for the 105 patients with pre-emptive therapy. Classic RRT was associated with a higher risk for mortality (adjusted odds ratio, 2.05; 95% CI, 1.03 to 4.09).⁸



In a randomised, controlled, two centre trial, a total of 106 ventilated severely ill mainly post surgery patients were randomised to early high-volume haemofiltration (72 to 96 L per 24 hours), early low-volume haemofiltration (24 to 36 L per 24 hours), or late low-volume haemofiltration (24 to 36 L per 24 hours). Early initiation was within 12 hours of oliguria (<30 ml/hour for six hours) and a creatinine clearance <20 ml/min. In the late group therapy was commenced after development of a traditional indication for renal therapy. There was no difference in survival at day 28 or renal recovery in any of the groups.¹¹

In a single-centre trial, 206 patients with acute kidney injury were randomised to early dialysis when serum urea nitrogen and/or creatinine levels increased to 25 mmol/L and 618 μ mol/L, respectively, whereas the control group received dialysis as per the renal team. Mean serum urea and creatinine levels were significantly higher in the control group. In-hospital mortality was 20.5% and 12.2% in the intervention and control groups, respectively (RR, 1.67; 95% CI, 0.88 to 3.17; P=0.2).²⁶

In a multi-centre, open-label pilot trial of critically ill adults with severe acute kidney injury defined as oliguria (<6 ml/kg for 12 hours), elevated creatinine (x2 baseline) and plasma NGAL >400 ng/ml, 101 patients were randomised to accelerated (12 hours or less from eligibility) or standard RRT initiation. Median serum creatinine and urine output at enrolment were 268 μ mol/l and 356 ml per 24 hours, respectively. In the accelerated arm, all patients commenced RRT and 45/48 did so within 12 hours from eligibility (median 7.4 hours). In the standard arm, 33 patients started RRT at a median of 31.6 hours from eligibility, of which 19 did not receive RRT. Mortality was 38% in the accelerated and 37% in the standard arm.¹²

In this multi-centre randomised trial 620 patients were randomised to early RRT, commenced at KDIGO stage three renal injury, or delayed therapy initiated for severe hyperkalemia, metabolic acidosis, pulmonary edema, blood urea nitrogen level higher than 40 mmol/L, or oliguria for more than 72 hours. Mortality at day 60 did not differ significantly between the early and delayed strategies (48.5% vs 49.7%; P=0.79). A total of 151 patients (49%) in the delayed-strategy group did not receive renal-replacement therapy. The rate of catheter-related bloodstream infections was higher in the early-strategy group than in the delayed-strategy group (10% vs 5%, P =0.03). Diuresis, a marker of improved kidney function, occurred earlier in the delayed-strategy group (P<0.001).¹⁴



Should we routinely start early renal replacement therapy in those with acute kidney injury?

Possibly not. The evidence remains unclear and further evidence is needed on the initiation of RRT in critical illness.

References

1. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med.* 2015; 41(8):1411-1423.
2. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S et al. Acute renal failure in critically ill patients: a multinational, multi-centre study. *JAMA* 2005; 294: 813-818.
3. Ricci Z, Ronco C, D'Amico G, De Felice R, Rossi S, Bolgan I, et al. Practice patterns in the management of acute renal failure in the critically ill patient: an international survey. *Nephrol Dial Transplant* 2006; 21: 690-696.
4. KDIGO AKI Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl.* 2012;2:1-138.
5. Bagshaw SM, Uchino S, Bellomo R, et al. Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury. *J Crit Care* 2009; 24: 129–140.
6. Shiao CC, Wu VC, Li WY, et al. Late initiation of renal replacement therapy is associated with worse outcomes in acute kidney injury after major abdominal surgery. *Crit Care* 2009; 13: R171.
7. Bagshaw SM, Wald R, Barton J, Burns KE, Friedrich JO, House AA, et al. Clinical factors associated with initiation of renal replacement therapy in critically ill patients with acute kidney injury—a prospective multi-centre observational study. *J Crit Care* 2012; 27(3):268-75.
8. Vaara ST, Reinikainen M, Wald R, Bagshaw SM, Pettilä V; FINNAKI Study Group. Timing of RRT based on the presence of conventional indications. *Clin J Am Soc Nephrol.* 2014; 9(9):1577-85.
9. Elseviers MM, Lins RL, Van der Niepen P, Hoste E, Malbrain ML, Damas P, et al. Sharf Investigators SH: Renal replacement therapy is an independent risk factor for mortality in critically ill patients with acute kidney injury. *Crit Care* 2010, 14: R221. 29.



10. Vinsonneau C & Monchi M: Too early initiation of renal replacement therapy may be harmful. *Crit Care* 2011, 15: 112.
11. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF & Kesecioglu J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomised trial. *Crit Care Med*. 2002; 30(10):2205-2211.
12. Wald R, Adhikari NK, Smith OM, Weir MA, Pope K, Cohen A et al; Canadian Critical Care Trials Group. Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. *Kidney Int*. 2015; 88(4):897-904.
13. Sugahara S, Suzuki H. Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery. *Hemodial Int*. 2004; 8(4):320-325.
14. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. *N Engl J Med* 2016; 375:122-133.
15. Karvellas CJ, Farhat MR, Sajjad I, Mogensen SS, Leung AA, Wald R et al. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. *Crit Care*. 2011;15(1):R72.
16. Chertow GM, Palevsky PM, Greene T. Studying the prevention of acute kidney injury: lessons from an 18th-century mathematician. *Clin J Am Soc Nephrol*. 2006; 1(5):1124-1127.
17. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A, NGAL meta-analysis Investigator Group: Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009; 54:1012–1024.
18. Cowland JB, Borregaard N: Molecular characterization and pattern of tissue expression of the gene for neutrophil gelatinase-associated lipocalin from humans. *Genomics* 1997; 45: 17–23.
19. Mårtensson J & Bellomo R. The Rise and Fall of NGAL in Acute Kidney Injury. *Blood Purif* 2014; 37:304–310.
20. Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, et al. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. *Arch Intern Med* 2007; 167:1655–63.
21. Lehner GF, Wiedermann CJ, Joannidis M. High-volume hemofiltration in critically ill patients: a systematic review and meta-analysis. *Minerva Anesthesiol* 2014; 80:595–609.



22. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet* 2000; 356:26–30.
23. Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008; 359:7–20.
24. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*. 2009; 361:1627–38.
25. Gettings LG, Reynolds HN, Scalea T. Outcome in posttraumatic acute renal failure when continuous renal replacement therapy is applied early vs late. *Intensive Care Med* 1999; 25(8):805-813.
26. Jamale TE, Hase NK, Kulkarni M, Pradeep KJ, Keskar V, Jawale S, et al. Earlier-start vs usual-start dialysis in patients with community-acquired acute kidney injury: a randomised controlled trial. *Am J Kidney Dis*. 2013; 62(6):1116-21.

Haematology Trials



IRONMAN

Litton E, Baker S, Erber W, Farmer S, Ferrier J, French C et al. Intravenous iron or placebo for anaemia in intensive care: the IRONMAN multi-centre randomised blinded trial. A randomised trial of IV iron in critical illness. *Intensive Care Med* 2016;42(11):1715-1722

Introduction

Anaemia is extremely common in the ICU, with 97% of patients becoming anaemic by day 8 of admission.¹ Epidemiological studies demonstrate an association between anaemia in critical illness and poor outcome.^{2,3} Although many critically ill patients can tolerate a restrictive transfusion strategy without adverse effects, anaemia is still the main indication in ICU for transfusion, which may itself be hazardous.^{4,5}

The aetiology of anaemia of critical illness is in part due to upregulation of hepcidin, an iron regulatory protein, reducing duodenal absorption of, and blocking macrophage release, of iron. This disrupts heme biosynthesis and leads to iron-restricted erythropoiesis.¹

The use of IV iron to treat anaemia in the ICU has been poorly studied to date but meta-analyses in the non-critically ill population suggests it may have the potential to improve haemoglobin (Hb) concentration and reduce the need for allogeneic blood transfusion.⁶ Conversely, iron is essential for bacterial proliferation and it has been hypothesized that the iron deficiency associated with inflammation may serve as a host protective mechanism.¹ Exogenous use of supplemental iron in the critically ill could, theoretically, increase the risk of bacterial infection. This trial sought to evaluate the efficacy and safety of IV iron in a critical care setting.

Study synopsis

This phase 2 multi-centre, blinded, randomised controlled trial was designed to assess if IV iron reduced the need for allogeneic blood transfusion and increased Hb concentration in ICU patients. Four ICUs in Perth, Australia, recruited adult patients admitted to ICU with an anticipated length of stay > 24 hours and with a Hb of < 100 g/L at any time in the preceding 24 hours. Recruitment was possible for up to 48 hours post-admission. Those with a transferrin saturation (TSAT) > 50%, and/or a ferritin level of > 1200 ng/ml, were excluded, as were patients with suspected or confirmed infection. Online permuted block randomisation, stratified by centre, was used to assign patients in a 1:1 ratio to either IV iron (500mg of ferric carboxymaltose in 100ml of 0.9% saline) or placebo (100ml of 0.9% saline). Four days after receiving study drug, if patients still met the laboratory inclusion criteria above, they could receive a repeat dose. Patients were assessed daily - if they continued to meet the inclusion criteria redosing was permitted until a maximum of 4 doses had been given.



The responsible treating clinician had control over all other aspects of patient management. None of the included study centres had a red cell transfusion policy. The primary outcome was the number of units of red cells transfused per patient between randomisation and hospital discharge. Secondary outcomes included Hb at hospital discharge and the proportion of patients who received a red cell transfusion. Adverse events and infection rates were also recorded.

The power calculation was based on an estimate from a prior observational study of a mean of 4 red cell transfusions in eligible patients. 140 patients were needed in order to detect a difference in the mean number of red cell transfusions of 1 unit between groups, with 80% power at the 5% significance level. Analyses were by intention-to-treat.

330 patients were assessed for eligibility. Most patients (28%) were excluded on the basis of high ferritin or TSAT levels. 24 of the 330 were excluded on the basis of suspected or confirmed infection (7%). 70 patients were enrolled in each group. Patients were well matched in terms of age, sex, APACHE II and SOFA score. Surgical admissions accounted for 87% (n=61) and 86% (n=60) of patients in the treatment and control groups, respectively. Cardiothoracic surgery (43%) and trauma (36%) accounted for the greatest number of reasons for admission in the treatment group and control groups, respectively. Two-thirds of patients in each group were mechanically ventilated and 70% were on vasoactive infusions at randomisation. More patients in the control group had received a red cell transfusion prior to randomisation, 26% vs 19%, but the median (IQR) number of units transfused prior to randomisation was low 1.5 (0-4). All patients received the assigned treatment and all were followed up to hospital discharge.

17 patients in the IV iron and 26 patients in the control group received repeat dosing of study drug. 10 patients received open-label IV iron (7 in the IV iron group and 3 in the control group), almost all on the ward after ICU discharge. There was no difference in the primary outcome of median number of red cell transfusions per patient in treatment vs control groups, 1 unit (0 to 2) vs 1 unit (0 to 3); P=0.53, incident rate ratio (IRR), 0.71; 95% CI, 0.43 to 1.18, P=0.19]. Although fewer red cells were transfused in the IV iron group compared with the control group, 97 v 136, this did not reach statistical significance. Adjustment for predefined baseline covariates, and using a per-protocol analysis, again demonstrated no significant between-group differences. Similarly, no significant difference was detected in the primary outcome for pre-defined subgroups of patients with TSAT < 20% and ferritin ≤ 200 ng/ml.

The median Hb at hospital discharge was higher in the IV iron group than the control group, 107 g/L (97 to 115) vs 100 g/L (89 to 111), (P=0.02). Length of stay and mortality rates in ICU and in-hospital were similar between groups. Infection rates were also similar. There were four serious adverse events in each group (2 DVT and 2 PEs each)



Study critique

This study aimed to contribute to the evidence base within the crucial area of transfusion practices in intensive care medicine. There are a number of potential explanations as to why no difference in the primary outcome was found.

Is the attempted restoration of iron stores in critically ill patients with evidence of iron deficiency overly simplistic and too linear as a therapeutic strategy? The erythropoietic response in critical illness, how it is modulated and influenced is an important subject that is enormously complex but not yet fully understood.

The transfusion of red cells in this study was not normally distributed. Results were presented in terms of median (IQR) rather than mean (SD) as initially planned. The power calculation relied on four transfusions in eligible patients, but the mean number of transfused units was much lower at 1.9 in the control group. Thus, the trial was underpowered to detect the 1 unit reduction in transfusion from a baseline of 4 that it had anticipated thus, raising the possibility of a type II error. On the basis of IRONMAN it is estimated that a future trial would need 1,572 patients to detect a mean change in red cell transfusion of 0.5 units at 80% power ($\alpha=0.05$).

The dosing of the drug, timing of first dose and duration of treatment may all have been insufficient to influence the primary outcome. Patients were permitted a maximum of 4 doses of study drug. The majority of patients (97) in this study received only 1 dose of study drug, with 38 patients receiving 2 doses, 5 patients receiving 3 doses and no patient receiving 4 doses. It is unclear if one dose can be expected to influence transfusion practices.

This was a study predominantly of surgical patients in ICU. 43% of the treatment group were admitted after cardiothoracic surgery. This particular surgical subgroup is likely to have undergone pre-operative optimization during which some of them may have been prescribed a course of oral or IV iron to optimize Hb. This may have influenced post-operative transfusion practices. Intra-operative blood conservation e.g. cell salvage, is not mentioned. In a study of transfusion practices in predominantly surgical ICU patients, the use of intra-operative cell salvage may have had a greater influence over post-operative transfusion of red cells than IV iron.

Although most patients were mechanically ventilated and on a vasoactive infusion at randomisation, the mean APACHE II score in the treatment and control groups was low at 12.2 (5.7) v 13.8 (6.1), respectively. The in-hospital mortality of 10% also indicates a relatively well cohort of ICU patients and suggests the results of this study are not generalizable to the overall ICU population. Septic patients were excluded.

Future studies will need to identify ICU patients who are at highest risk of blood



transfusion e.g. by utilising a lower Hb trigger for inclusion and a longer length of ICU stay. The participating units in this trial did not have red cell transfusion protocols or triggers. Transfusion was left to the discretion of the treating clinician. With a mean Hb prior to transfusion, of 76 g/L and 75 g/L, in the treatment and control groups, respectively, it would appear that a more restrictive transfusion policy perhaps with a trigger of 70 g/L could have been adopted. A lower transfusion trigger may be a more effective strategy at reducing red cell transfusion than IV iron.

Where this sits in the body of evidence

In an attempt to investigate the effect of IV iron therapy on critically ill trauma patients, Pieracci et al randomised patients to either IV iron (iron sucrose 100mg three times per week for up to 2 weeks) or placebo.⁷ This single-blinded, multi-centre, randomised controlled study was carried out in 4 trauma centres in the US and included 150 patients. The Hb threshold for inclusion in this trial was 12 g/dL and patients needed to have a predicted ICU length of stay of > 5 days. 57 (38%) patients received all 6 doses of study drug. Although IRONMAN used a higher dose of iron and had a lower Hb trigger for inclusion (10 g/dL), this study examined a more homogenous patient group with higher APACHE II scores, median 23.1 (5 to 41) v 20.9 (0 to 40), in treatment and control groups, respectively. No difference in Hb concentration, transferrin saturation or requirement for red cell transfusion was detected between groups.

The CRIT study was a prospective, multi-centre observational study, aiming to ascertain the incidence of anaemia and red cell transfusion in ICUs across the US.³ 284 ICUs in 213 hospitals contributed to the data set on 4,892 patients. By 48 hours post admission 70% of patients had a Hb < 12 g/dL. A Hb of < 9g/dL was an independent predictor of increased mortality. 44% of patients received at least 1 red cell transfusion during their ICU stay with the number of transfusions independently associated with a longer length-of-stay in ICU and hospital and a higher mortality.

A European prospective, multi-centre observational study, collected data over a two week period on patterns of blood sampling, anaemia and red cell transfusion across 146 Western European ICUs.² 1,136 patients contributed to the blood sampling and 3,534 patients to the anaemia and red cell transfusion data sets, respectively. A mean (SD) volume of blood of 41.1 (39.7) ml was venesected in a 24 hour period. Sicker patients tended to have greater frequency of blood sampling. 29% of patients had a Hb < 10g/dL on admission. 37% of patients received a blood transfusion. Transfusion was associated with a higher ICU and hospital mortality.

A systematic review (75 studies) and meta-analysis (72 studies) of randomised controlled trials investigated the safety and efficacy of IV iron in a range of clinical settings. IV iron did increase Hb concentration (standardized mean difference 6.5 g/dL (95% CI, 5.1 g/dL to 7.9 g/dL) and reduced the risk of red cell transfusion, risk ratio 0.74 (95% CI, 0.62 to



0.88). A significantly increased risk of infection was associated with the use of IV iron, relative risk 1.33 (95% CI, 1.10 to 1.64). There was significant heterogeneity between studies with different IV iron preparations and doses used. Furthermore, there was a paucity of studies included which had been carried out in the critical care environment.⁶

The use of erythropoietin (EPO) in the preceding 3 months was an exclusion criterion for IRONMAN. In a multi-centre, prospective, randomised, placebo-controlled trial, 1,460 patients from a mixed medical-surgical ICU background, were randomised to receive either EPO or placebo. The aim was to assess if the use of EPO reduced the percentage of patients requiring red cell transfusions and/or increased Hb concentration. 40,000 units of EPO or placebo was given weekly for three weeks and patients followed up for 140 days. No difference in the number of red cell transfusions or of percentage of patients transfused was detected. At day 29, Hb concentration was higher in the EPO group compared with placebo (1.6 ± 2 g/dL vs 1.2 ± 1.8 g/dL), $P < 0.001$. The EPO group had a higher rate of thrombosis than placebo (HR, 1.41, 95% CI, 1.06 to 1.86).⁸

Should we routinely use erythropoietin as a blood transfusion sparing therapy?

No. At present there is no evidence for the use of IV iron to reduce red cell transfusion in the ICU patient.

References

1. Hayden SJ, Albert TJ, Watkins TR, Swenson ER. Anemia in critical illness: insights into etiology, consequences, and management. *Am J Respir Crit Care Med* 2012;185(10):1049–57.
2. Vincent JL, Baron J-F, Reinhart K, Gattinoni L, Thijs L, Webb A, et al. Anemia and blood transfusion in critically ill patients. *JAMA* 2002;288(12):1499–1507.
3. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, et al. The CRIT Study: anemia and blood transfusion in the critically ill-current clinical practice in the United States. *Crit Care Med* 2004;32(1):39–52.
4. Herbert PC, Wells G, Blajchman MA, et al. A multi-centre, randomised, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999;340(6):409–417.
5. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med* 2014;371(15):1381–1391.
6. Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. 2013 [cited 2016 Nov 7]; Available from:



<http://www.bmj.com/content/347/bmj.f4822.full>

7. Pieracci FM, Stovall RT, Jaouen B, et al. A multi-centre, randomised clinical trial of IV iron supplementation for anemia of traumatic critical illness. *Crit Care Med* 2014;42(9):2048–2057.
8. Corwin HL, Gettinger A, Fabian TC, et al. Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med* 2007;357(10):965–976.

Sepsis Trials



SEPSIS 3

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315(8):801-810

Introduction

Sepsis remains a major cause of morbidity and mortality, and vast consumer of healthcare resources. In the USA, its incidence is 300 per 100 000 of the population,¹ and had an annual cost of 24 billion dollars a decade ago.² Mortality rises as sepsis worsens, from approximately 25% with severe sepsis to 50% with septic shock.¹

As one quarter of cases of severe sepsis occur outside the ICU,¹ early recognition has the potential to dramatically improve outcome and healthcare utilisation. With no biomarker yet available for the identification of infection, clinical sepsis research proceeds in populations with suspected or proven infection. A vital part of this work is the recognition of infection-related physiological perturbation at the earliest opportunity.

The first sepsis definition (Sepsis 1)³ was produced in 1991 and updated in 2001 (Sepsis 2).⁴ These definitions were largely inflammation-based, with Sepsis 1 founded upon the requirement of two of four systemic inflammatory response syndrome (SIRS) criteria and Sepsis 2 adding clinical and laboratory parameters for the recognition of inadequate organ perfusion. Over the following 15 years, numerous advances have been made in the pathobiology of this syndrome, combined with a gradually falling mortality rate.⁵

Amongst the advances has been the realisation that SIRS both lacks sufficient specificity for the identification of sepsis and misses one-in-eight patients with likely infection in the ICU.⁵ Clinical trials enrolling patients with presumed sepsis, using SIRS as an inclusion criterion, risk significant heterogeneity and resulting null results. Uninfected patients meeting SIRS criteria may be subjected to unnecessary, potential harmful antibiotics and suffer delayed diagnosis of the true illness. Similarly, septic patients may not meet the necessary SIRS criteria yet have significant infection and be misdiagnosed and mistreated. To address these issues, an updated definition (Sepsis 3) was formulated.

Study synopsis

There were 4 steps in the formulation of the new SEPSIS 3.0 definition:⁶⁻⁸

1. the creation of the task force
2. a systematic review of the literature, to identify clinical criteria currently used to identify sepsis and inform a delphi process
3. a delphi process, to achieve consensus on new sepsis and septic shock definitions, plus clinical criteria to identify them
4. validation of the new sepsis definitions using three electronic databases



The European Society of Intensive Care Medicine and the Society of Critical Care Medicine each nominated a co-chair to convene a task force to update the definitions of sepsis and septic shock. In January 2014, the two co-chairs invited 17 specialists in critical care, infectious disease, surgery, and respiratory medicine, predominantly from North America and Europe, and one from Australia, who had expertise in sepsis epidemiology, clinical trials and translational science, to join the group. Although the task force was funded by the two societies, it maintained autonomy, and was independent of industry involvement. Over a one year period, up to January 2015, the task force met four times and also corresponded by email.

The systematic review sought to identify clinical criteria currently used to identify sepsis and septic shock and determine whether these differing criteria were associated with varying outcomes. MEDLINE was searched using search terms, MeSH headings and the term "sepsis", "septic shock" and "epidemiology". Results were limited to observational studies in adults, reported in English between January 1992 and December 2015. Randomised controlled trials were excluded, due to limitations with generalisability, as were patient- or pathogen-specific studies and before-and-after trials. Forty-four studies reporting septic-shock specific mortality were included. Study data was extracted for use in the Delphi process.

The Delphi process consisted of three face-to-face meetings and three rounds of questionnaires, in addition to ongoing email correspondence. The results of the systematic reviews were made available to all task force members. The three rounds of questionnaires took place in August, November and January. These sequentially addressed the components of the definitions, key terms and predictive ability, and agreement on the final constitution of the new definitions. A 65% agreement was required to accept items discussed in this process, with items scoring below this dismissed or rediscussed to achieve a unified opinion.

From a heterogenous set of 44 studies, the septic shock-associated crude mortality was 46.5% (95% CI, 42.7% to 50.3%) The Delphi process established three variables, hypotension, serum lactate level, and vasopressor therapy, to test in electronic health records. Six combinations of these variables were tested in the Surviving Sepsis Campaign database (2005 to 2010; n = 28 150), with the highest mortality (42.3%; 95% CI, 41.2 to 43.3%) being in a group fluid resuscitated yet still requiring vasopressors to maintain a mean arterial blood pressure \geq 65 mm Hg and being hyperlactaemic ($>$ 2 mmol/L). These results were then externally validated in two further electronic health records, the University of Pittsburgh Medical Center (2010 to 2012; n = 1,309,025), and Kaiser Permanente Northern California (2009 to 2013; n = 1,847,165).

| Definitions | |
|--------------|---|
| Sepsis | Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection |
| Septic Shock | Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality |

Table 3: The 2015 definitions of sepsis and septic shock

| Identifying Clinical Criteria | |
|-------------------------------|---|
| Sepsis | Suspected or documented infection and an acute increase of ≥ 2 SOFA points |
| Septic Shock | Sepsis and vasopressor therapy needed to elevate MAP ≥ 65 mm Hg and lactate > 2 mmol/L (18 mg/dL) despite adequate fluid resuscitation |

Table 4: The clinical criteria used to recognise sepsis and septic shock

The definitions of sepsis and septic shock were separated from the clinical criteria used to identify them. Without a specific biomarker for infection, the identification of sepsis remains the recognition of organ dysfunction in the setting of known or presumed infection. The best fit for the recognition of organ dysfunction came from an increase in the SOFA score (sequential organ failure assessment) of at least 2 points. Outside of an ICU, a modified quick SOFA score (qSOFA) could be undertaken, which provides a screen for organ dysfunction without advanced diagnostics, such as plasma lactate levels. The term “severe sepsis” is now deemed redundant and the SIRS criteria removed.

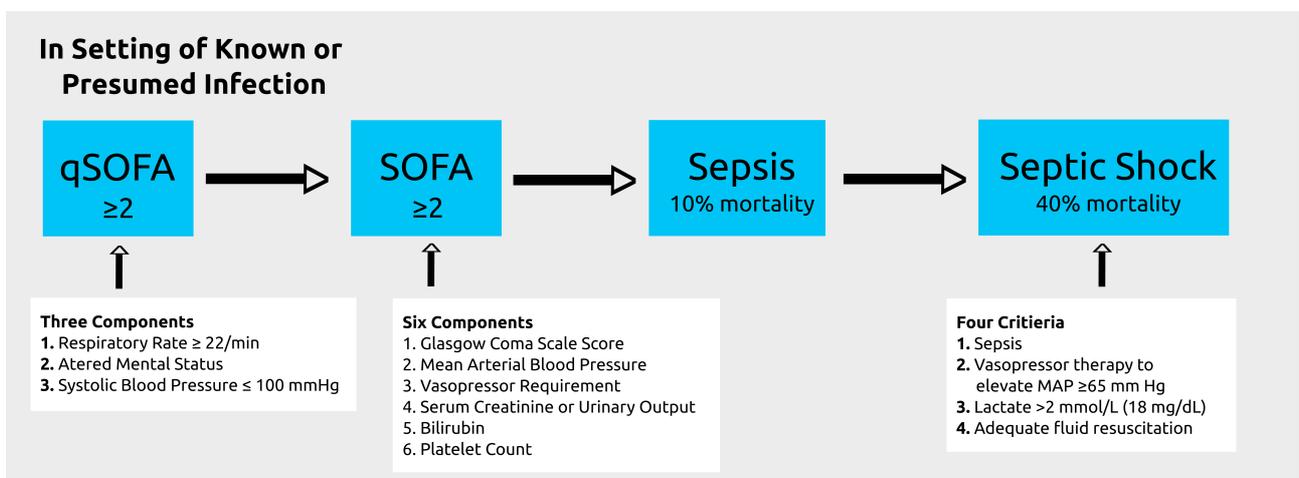


Diagram 1: The operationalisation of sepsis

Once the work of the task force was complete, their recommendations and findings were disseminated to major international societies and bodies for endorsement.

Study critique

The process of updating the 2001 Sepsis 2 definition⁴ was a large undertaking completed in a methodical fashion by a group of globally renowned experts. By using a systematic review to determine the current sepsis landscape and incorporate the latest changes in sepsis pathobiology, a Delphi process to agree which variables to test, and constructive and external validative modeling in existing large electronic databases, sepsis 3.0 could improve on the known limitations of the SIRS-based Sepsis 2 definition from 15 years ago. This updated definition will provide an enhanced framework for ongoing research in the field. In due course, as our understanding of sepsis progresses, these guidelines will be updated again. However, at present, few publications in 2016 have generated as much controversy as this group of papers.^{9,10}

Despite being a major achievement, a landmark, and difficult, project such as this is not without its issues. The biggest remains the inability of any clinical criteria to determine whether infection is present. Arguably, Sepsis 2, which detected physiological perturbations, has been superseded by a more specific organ dysfunction recognition tool. Both models recognise physiological disturbance, but neither help clarify whether infection is the cause. In addition, the sensitivity of SIRS appears to have been traded for the specificity of qSOFA/SOFA. This could become a problem when used as an early warning system, as an increased specificity could equate to more accurate identification of a sicker cohort of patients, sicker because they are identified later, and thus have a worse outcome. Early identification, where therapy may be most efficacious, may be lost by waiting for the signs of organ dysfunction to develop.

The age old predicament for a definition of any syndrome is its lack of specificity due to the absence of a gold standard test for the presence of the condition. The criteria described by the Berlin ARDS definition encompasses a vast range of conditions, 50% of which are without the pathognomic histological feature of diffuse alveolar damage.¹¹ Imprecise definitions lead to heterogenous cohorts being recruited into trials and subsequent findings of no difference for any therapeutic intervention. It is unsurprising the major advances in ARDS relate to mitigation or avoidance of ventilator-induced lung injury, rather than any ARDS-related biological target. Therapeutic advances in sepsis have similarly proven difficult to make, with just one positive,¹² although controversial, breakthrough subsequently reversed through a number of randomised controlled trials failing to replicate the original findings, even in the sickest patients.

Whilst the variables identified by the Delphi process were examined in 6 different combinations in the Surviving Sepsis Campaign database, this database itself suffers from the limitations of identifying true infection-related organ dysfunction. The



subsequent database validations are vulnerable to the same problem. One commentator has described the retrospective database validation technique as being *“non sequitur, having used a sophisticated retrospective analysis to demonstrate that the presence of organ dysfunction, as detected by a SOFA score, optimises the combined sensitivity and specificity for life-threatening organ dysfunction”*.¹³

The use of big data also suffers another limitation – they are largely American & German based, despite the majority of sepsis worldwide being in the developing world, and especially sub-saharan Africa. The development of qSOFA allows a simple screen for the recognition of organ dysfunction, with most healthcare systems having a blood pressure monitor of some variety. In addition to its geographical restraint in terms of validation, of the 19 task force members, none were from low and middle income countries, where the mortality from sepsis remains appreciably higher.¹⁴

Despite utilising a systematic approach and validating the operationalisation of the definitions in large electronic databases, this work has not been universally welcomed. Several national bodies have declined to endorse the use of qSOFA / SOFA for the identification of sepsis; in the UK, the Royal College of Emergency Medicine, NICE and the UK Sepsis Trust do not recommend the use of qSOFA at this time, while several major American bodies also fail to do so, including the American College of Emergency Physicians,¹³ the Infectious Disease Society of America and various Emergency Medicine bodies. Low and Middle Income Countries have also expressed disappointment with this definition.¹⁵ SIRS-based sepsis screening has long been taught and is deeply embedded in many healthcare systems. Changing to qSOFA-based screening will require large scale educational campaigns and uptake of this new construct, a move not helped by the lack of a clear advantage with the newer model, given most working clinically are comfortable with the older model.

Regardless of intellectual feelings towards Sepsis 3, the task force has worked diligently to progress the care we deliver to patients with infection-related organ dysfunction. The need to embrace uncertainty in an uncertain world, allied with doing the best with what we have, appears a logical conclusion.¹⁰

Where this sits in the body of evidence

Sepsis 2, based on the presence of two or more SIRS criteria, is a sensitive, but not specific tool for the identification of sepsis, or more accurately, the presence of physiological disturbance in the likely setting of infection. In an evaluation of the SOAP study, including all 3147 new admissions to 198 ICUs across 24 European countries in a two week period in May 2002, 93% of patients met two SIRS criteria at least once during their ICU stay, while 87% met two criteria at the time of their admission. As the number of SIRS criteria increased, so too did morbidity and mortality.¹⁶



Kaukonien and colleagues retrospectively reviewed data from 1,171,797 patients admitted to 172 Australian or New Zealand intensive care units between 2000 and 2013 and found 109,663 had infection and organ failure. In this group, 13,278 patients (12.1%) had SIRS-negative sepsis. Mortality increased with the addition of each SIRS criterion (odds ratio, 1.13; 95% CI, 1.11 to 1.15; P<0.001) without any increase in risk at a threshold of two SIRS criteria.⁵

Cherpek and colleagues completed a single centre retrospective review, evaluating all 30,677 patients with suspected infection in the emergency department or wards from 2008 to 2016. The test characteristics of qSOFA were compared with SIRS, MEWS (modified early warning system) and NEWS (national early warning system). Based on the cut-off values for each model, the combined mortality & ICU transfer sensitivity and specificity was calculated. The accuracy for the prediction of mortality was determined using the highest non-ICU scores recorded. The combined outcome was reached 12 hours earlier in patients with SIRS ≥ 2 than qSOFA ≥ 2 (17 vs 5 hours).¹⁷

| Test Characteristics | | | | | |
|----------------------|--------------------------|-------------|-------|-----------|--------------|
| | Mortality & ICU Transfer | | | Mortality | |
| | sensitivity | specificity | | AUC | 95% CI |
| SIRS ≥ 2 | 91% | 13% | SIRS | 0.65 | 0.63 to 0.66 |
| qSOFA ≥ 2 | 54% | 67% | qSOFA | 0.69 | 0.67 to 0.70 |
| MEWS ≥ 5 | 59% | 70% | MEWS | 0.73 | 0.71 to 0.74 |
| NEWS ≥ 8 | 67% | 66% | NEWS | 0.77 | 0.76 to 0.79 |

Table 5: Test characteristics of SIRS, qSOFA, MEWS and NEWS¹⁷

Should we change to qSOFA / SOFA for the recognition of sepsis?

This may depend on setting. Few ICU clinicians base their determination of the presence or absence of sepsis on SIRS criteria. As such, this definition will make little difference. SOFA and antimicrobial data will be captured in most electronic patient care systems allowing epidemiological data to be collected. Outside the ICU, low and middle income countries fear a lack of sensitivity with qSOFA, while those in better resourced healthcare systems need to implement this in a consistent, systematic and rigorous manner. Individual uptake of the definition within an institution may lead to care of varying quality.



References

1. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. *Virulence* 2014;5(1):4–11.
2. Lagu T, Rothberg MB, Shieh M-S, Pekow PS, Steingrub JS, Lindenauer PK. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. *Crit Care Med* 2012;40(3):754–61.
3. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;101:1644–55.
4. Levy MM, Fink MP, Marshall JC, et al. 2001 sccm/esicm/accp/ats/sis international sepsis definitions conference. *Intensive Care Med* 2003;29(4):530–8.
5. Kaukonen K-M, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *Jama* 2014;311(13):1308–16.
6. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315(8):801–10.
7. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315(8):762–74.
8. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (sepsis-3). *Jama* 2016;315(8):775–87.
9. Cortés-Puch I, Hartog CS. Opening the Debate on the New Sepsis Definition Change Is Not Necessarily Progress: Revision of the Sepsis Definition Should Be Based on New Scientific Insights. *Am J Respir Crit Care Med* 2016;194(1):16–8.
10. Angus DC. Opening the Debate on the New Sepsis Definition Defining Sepsis: A Case of Bounded Rationality and Fuzzy Thinking? *Am J Respir Crit Care Med* 2016;194(1):14–5.
11. Thille AW, Esteban A, Fernández-Segoviano P, et al. Comparison of the Berlin Definition for Acute Respiratory Distress Syndrome with Autopsy. *Am J Respir Crit Care Med* 2013;187(7):761–7.
12. Bernard GR, Vincent J-L, Laterre P-F, et al. Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis. *N Engl J Med* 2001;344(10):699–709.
13. Simpson SQ. New Sepsis Criteria: A Change We Should Not Make. *Chest* 2016;149(5):1117–8.
14. Dünser MW, Festic E, Dondorp A, et al. Recommendations for sepsis management in



resource-limited settings. *Intensive Care Med* 2012;38(4):557–74.

15. Machado FR, Salomão R, Azevedo P de, Lisboa T, Filho R, on behalf of t. Why (the) Latin American Sepsis Institute did not endorse the new definitions of sepsis published today in JAMA. [cited 2017 Jan 6]; Available from: ilas.org.br/assets/arquivos/upload/statement-en.pdf
16. Sprung CL, Sakr Y, Vincent J-L, et al. An evaluation of systemic inflammatory response syndrome signs in the Sepsis Occurrence in Acutely ill Patients (SOAP) study. *Intensive Care Med* 2006;32(3):421–7.
17. Churpek DMM, Snyder MA, Han DX, et al. qSOFA, SIRS, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients Outside the ICU. *Am J Respir Crit Care Med* 2016; epublished September 20th



LeoPARDS

Gordon AC, Perkins GD, Singer M, McAuley DF, Orme RML, Santhakumaran et al. Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis. *N Engl J Med* 2016;375:1638-1648

Introduction

In a retrospective analysis of 101,064 patients from the ANZICS database, from 2000 to 2012, the prevalence of severe sepsis or septic shock on admission to the ICU was 9.7%.¹ Despite a falling mortality associated with severe sepsis and septic shock over this time period, the 2012 fatality rate remains high at 18.4%. In the USA, 230,000 people suffer from septic shock annually and 40,000 die.²

Catecholamines are widely used for the preservation of arterial blood pressure in the setting of septic shock, with noradrenaline the most commonly used agent in recent large, multi-centre randomised controlled trials.³ However, catecholaminergic therapy is not without risk and carries the possibility of tachycardia, increased myocardial and whole body energy expenditure, insulin resistance, hyperglycaemia, splanchnic and digital ischaemia, as well as various pro-infectious mechanisms including facilitating iron transfer from lactoferrin and transferrin to bacteria.⁴ The search for a non-catecholaminergic agent for use in septic shock has led to both vasopressin, a vasopressor peptide secreted by the posterior pituitary, and levosimendan, a novel calcium-sensitising inodilator. In addition to improving myocardial contractility without increasing myocardial energy demand, levosimendan has numerous extra-cardiac effects, including being anti-inflammatory, anti-apoptotic, anti-vasospastic, improving gut perfusion, and limiting ischaemia-reperfusion injury. These actions have been suggested to protect the brain, spinal cord, heart, lung, diaphragm, liver, kidney and gut.⁵

Study synopsis

LeoPARDS was a UK multi-centre, double-blind, parallel group, randomised controlled trial examining whether levosimendan reduced the severity of organ failure in adults with early septic shock. The trial was funded by the National Institute for Health Research and Tenax Therapeutics, sponsored by Imperial College London and the study drugs were provided free of charge by Orion Pharma. None of these entities had input into the design, conduct, analysis or reporting of the trial.

Adults with septic shock, despite adequate fluid resuscitation and requiring vasopressor support for at least 4 hours, were eligible for enrolment. Exclusion criteria were vasopressor support for greater than 24 hours, pre-existing dialysis dependence, Child-Pugh class C liver impairment, mechanical ventricular obstruction, treatment limitations, severe obesity (>135 kg), pregnancy, receipt of levosimendan within 30 days, allergy to levosimendan or enrolment in another investigational trial within 30 days. Randomisation



was performed via a web-based system with patients assigned in a 1:1 fashion to levosimendan or placebo groups, in variable block sizes of 4 and 6, stratified for centre. Study drugs were identically presented.

Patients received a continuous infusion of levosimendan or placebo for 24 hours. In addition to standard therapy. The study drug was commenced at 0.1 µg/kg/min and increased after 2 to 4 hours to 0.1 µg/kg/min for the remainder of a 24 hour period, after which the infusion was stopped. If rate limiting side effects, such as hypotension or tachycardia (>130 bpm), occurred the infusion was decreased in a specified manner and could ultimately be stopped. Both groups were managed as per local clinical practice and based on the surviving sepsis campaign guidelines. Dobutamine was recommended as first choice inotrope and vasopressors were to be administered at the lowest possible dose.

The primary outcome was the mean daily SOFA (sequential organ failure assessment) score, excluding the neurological component, while the patient was in ICU and up to a maximum of 28 days. Secondary outcomes included individual SOFA components, catecholamine-free days, ventilator-free days, time to weaning from mechanical ventilation, the proportion of patients with a major acute kidney event, duration of renal replacement therapy, lengths of stay in ICU and hospital, and mortality at various endpoints. Five hundred patients were required to detect a between group difference of 0.5 points in the mean SOFA score with a power of 90% at the 5% significance level and assuming a standard deviation of 1.5 points. Allowing for a 3% consent withdrawal rate, the target sample size was 516 patients. Analysis of the primary outcome was on an unadjusted intention-to-treat basis.

2,382 patients were screened and 516 patients were recruited over a 24 month period from January 2014 to December 2015, with 259 assigned to levosimendan and 257 to placebo. The most common exclusion criteria were being outside the 24 hour inclusion period (n=714) and treatment limitations (n=352). One patient in the levosimendan withdrew consent and was not included in the analysis. Groups were similar at baseline, with both having median APACHE II scores of 25 and SOFA score of 10. 56% were male, 93% were Caucasian and the median ages were 67 (levosimendan) and 69 (placebo). Almost all patients were receiving a noradrenaline infusion at recruitment, at median doses of 0.29 (levosimendan) and 0.27 (placebo) µg/kg/min, resulting in mean arterial pressures of 74 and 73 mm Hg, respectively. Small numbers of patients were also receiving adrenaline, vasopressin or dobutamine infusions. The median time from commencement of a vasopressor to trial recruitment was 16 hours.

At 24 hours, levosimendan administration resulted in a lower blood pressure, higher heart rate and greater noradrenaline requirement. There was no difference in fluid administration, stroke volume, cardiac index or lactate levels (table 6). Levosimendan

was discontinued more often due to hypotension or tachycardia (13.5% vs 7.7%).

There was no statistically significant difference in the primary outcome, the mean (SD) SOFA score recorded in ICU {levosimendan 6.68 (3.96) vs placebo 6.06 (3.89); mean difference, 0.61; 95% CI, -0.07 to 1.29; P = 0.053}. In an analysis of SOFA components independent of each other, the levosimendan group had a higher cardiovascular component score (mean difference, 0.25; 95% CI, 0.04 to 0.46; P=0.01). There was no difference in 28 day mortality (levosimendan 34.5% vs placebo 30.9%; mean difference, 3.6% ; 95% CI, -4.5 to 11.7; P=0.43). Those receiving levosimendan were less likely to have weaned from mechanical ventilation at 28 days (hazard ratio, 0.77; 95% CI, 0.60 to 0.97; P=0.03). There were more adverse events in the levosimendan group (32 vs 23), with supraventricular tachycardia being more common with the intervention.

| | Levosimendan | Placebo | Difference (95% CI) |
|---------------------------------------|-------------------|-------------------|---------------------|
| MAP (mm Hg) | 73 (11) | 78 (12) | -5 (-7 to -3) |
| Heart Rate (bpm) | 102 (22) | 89 (19) | 13 (9 to 16) |
| Noradrenaline (µg/kg/min) | 0.28 (0.14, 0.46) | 0.18 (0.07, 0.33) | 0.10 (0.06 to 0.15) |
| Fluid Administered (ml) | 1847 (272, 2518) | 1718 (1176, 2540) | 129 (-140 to 304) |
| Lactate (mmol/L) | 1.4 (1.1, 2.1) | 1.7 (1.1, 2.2) | -0.3 (-0.4, 0.0) |
| Stroke Volume (ml) | 63 (49, 83) | 72 (61, 83) | -9 (-18, 0) |
| Cardiac Index (L/min/m ²) | 3.5 (1.4) | 3.3 (1.0) | 0.2 (-0.2, 0.6) |

Table 6: Circulatory variables in LeoPARDS

Mean arterial pressure, heart rate, stroke volume and cardiac index reported as mean (SD); noradrenaline, fluid administered and lactate reported as median (IQR).

Study critique

Despite a plethora of preclinical and small phase II trials demonstrating beneficial mortality and cardiac effects of levosimendan in sepsis,⁶ in this robust randomised controlled trial in critically ill patients, levosimendan not only failed to show evidence of inotropy, but resulted in worse circulatory SOFA scores and a longer duration of mechanical ventilation. How could such an unexpected result occur?

The population was appropriately identified, being high risk with a 30.9% control group mortality and, received the intervention sufficiently early, within 20 hours of the requirement for vasopressor support. Although the target dose of levosimendan was similar to that of previous trials, aiming for 0.2 µg/kg/min, given the more robust nature of LeoPARDS, this may have been the first trial to identify possible toxicity in a critically ill septic population. With more patients in the levosimendan group discontinuing the study drug due to adverse haemodynamic effects, and no signal of increased inotropy with a supposed inotropic agent, the pharmacodynamics of this drug in critically ill septic



patients may need to be revised. Although more patients in the control group received dobutamine, potentially lessening any inotropic difference, the total number was less than 10%. Similarly, there was no outcome difference in patients with the lowest cardiac index. Unfortunately, echocardiographic measurements of cardiac function were not undertaken, somewhat limiting the interpretation of the cardiovascular effects. The exact nature of the likely toxicity of levosimendan in critically ill patients with sepsis is uncertain, but could possibly be related to calcium handling, elevated myocardial energy demand related to tachycardia or excessive venodilation.

The primary aim of LeoPARDS was to assess the effect of levosimendan on organ dysfunction in patients with septic shock. Thus, the focus was not limited to its inotropic actions but also included its extra-cardiac effects. Disappointingly, there was no signal of benefit in any SOFA component or other organ-specific endpoint.

A 2015 meta-analysis of 7 trials investigating levosimendan in sepsis reported a strong beneficial effect on mortality (47% vs 61%; RR, 0.79; 95% CI, 0.63 to 0.98).⁷ This effect was lost in sensitivity analyses excluding studies at high risk of bias. As ever with meta analyses, detailed consideration of the included studies is required to draw valid comparisons. These trials were all small, with an average of just 35 patients each, mostly single-centre, and largely compared levosimendan with dobutamine, rather than placebo. Of course, this questions the comparative effect of dobutamine versus placebo in the management of sepsis. A larger general meta-analysis including cardiac surgical trials, was also published in 2015.⁸ In a review of sepsis trials alone, there was also a suggestion of a mortality benefit with levosimendan, which again was lost when analysis was limited to trials at low risk of bias (RR 0.83, adjusted 95% CI, 0.48 to 1.55). Interestingly, a review of 25 meta analyses, including over 6000 patients, suggested that levosimendan did show clear signs of benefit. An alternative view of this article is that we need less meta analyses of small trials and more large, robust, multi-centre randomised controlled trials.⁹

Levosimendan increased heart rate and decreased blood pressure despite a higher noradrenaline dose, with signals of a lower stroke volume. However, the cardiac index was higher, due to the tachycardic effects of this drug. This increase in cardiac index was also seen in previous studies examining this variable. There is a school of thought dichotomising cardiac index/output into adequate and inadequate, rather than based on any numerical value. As such, the artificial elevation of cardiac index through a chronotropic effect runs counter to the contemporary issue of whether β blockade induced slowing of heart rate is beneficial in septic shock.¹⁰

One of the few weak points of LeoPARDS is its choice of primary outcome, mean SOFA score. This is disappointing given the otherwise excellent design and conduct of the trial. As a strong pragmatic trial, the results of LeoPARDS are generalisable to any population

of patients with septic shock meeting the inclusion and exclusion criteria and managed in a similar healthcare system. Based on LeoPARDS, levosimendan currently has no role in the treatment of sepsis. Whether it has a role in septic patients with myocardial dysfunction requires a further trial, although it is questionable if equipoise still exists. The place of levosimendan in the management of non-septic myocardial dysfunction is not addressed by this trial, with trials ongoing in both cardiac surgery and cardiology.⁹

Where this sits in the body of evidence

A second, smaller randomised controlled trial evaluating levosimendan was also published in 2016, comparing this agent with dobutamine in 38 patients with fluid resuscitated septic cardiomyopathy and an ejection fraction of <45%. Patients received 24 hour infusions of either levosimendan at 0.2 µg/kg/min or dobutamine at 5 µg/kg/min. Despite superior mechanical cardiac values and lower values of biochemical markers of myocardial injury, there were no between group differences in patient centred outcomes, including days on mechanical ventilation, length of stay in ICU and hospital, or 28-day mortality (levosimendan 31.6% vs dobutamine 36.8%; P=0.732)¹¹

Zangrillo and colleagues meta analysed seven small randomised controlled trials, including 246 patients with severe sepsis or septic shock, comparing levosimendan with control. Levosimendan was associated with improved mortality, a lower blood lactate level, higher cardiac index, greater fluid loading, and unchanged mean arterial pressure and noradrenaline dosing.⁷

Morelli and colleagues completed a small, single-centred, open label, randomised controlled trial comparing esmolol with placebo in 154 tachycardiac patients with septic shock requiring noradrenaline. Esmolol was titrated to achieve a heart rate between 80 and 94 bpm, while the control group remained tachycardiac with a heart rate of approximately 105 bpm. 49.4% of patients treated with esmolol, and 40.3% of control patients, received rescue levosimendan (P =0.39). β blockade resulted in a higher stroke volume, reduced requirement for noradrenaline and lower. 28 day mortality (49.4% vs 80.5%; P<.001).

Whether inotropy should be used in acute decompensated heart failure remains to be proven. A pre-LeoPARDS meta-analysis including 28,280 patients from 177 randomised controlled trials recently examined the effects of inotropes and vasopressors on mortality.¹² Reviewing 24 trials of acute heart failure, there was no difference in mortality (inotrope/vasopressor 13.5% vs control 11.6%; RR with control 0.91; 95% CI, 0.78 to 1.07; P=0.26). Results were similar considering all inotropic agents (22.4% vs 22.2% mortality, respectively; RR 0.97; 95% CI, 0.93 to 1.10; P=0.18). Interestingly, levosimendan was the only inotrope to show a beneficial effect on mortality. The data at present continue to largely fail to demonstrate efficacy from inotropic agents in this setting. LeoPARDS is consistent with this theme.



Should we use levosimendan in septic shock?

No, in the absence of compelling new data, levosimendan has no role in the general management of patients with septic shock.

References

1. Kaukonen K-M, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA* 2014;311(13):1308–16.
2. Seymour CW, Rosengart MR. Septic shock: advances in diagnosis and treatment. *JAMA* 2015;314(7):708–17.
3. Angus DC, Barnato AE, Bell D, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. *Intensive Care Med* 2015;41(9):1549–60.
4. Singer M. Catecholamine treatment for shock—equally good or bad? *The Lancet* 2007;370(9588):636–7.
5. Farmakis D, Alvarez J, Gal TB, et al. Levosimendan beyond inotropy and acute heart failure: Evidence of pleiotropic effects on the heart and other organs: An expert panel position paper. *Int J Cardiol* 222:303–12.
6. Pierrakos C, Velissaris D, Franchi F, Muzzi L, Karanikolas M, Scolletta S. Levosimendan in critical illness: a literature review. *J Clin Med Res* 2014;6(2):75.
7. Zangrillo A, Putzu A, Monaco F, et al. Levosimendan reduces mortality in patients with severe sepsis and septic shock: A meta-analysis of randomised trials. *J Crit Care* 30(5):908–13.
8. Koster G, Wetterslev J, Gluud C, et al. Effects of levosimendan for low cardiac output syndrome in critically ill patients: systematic review with meta-analysis and trial sequential analysis. *Intensive Care Med* 2015;41(2):203–21.
9. Pollesello P, Parissis J, Kivikko M, Harjola V-P. Levosimendan meta-analyses: Is there a pattern in the effect on mortality? *Int J Cardiol* 209:77–83.
10. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomised clinical trial. *Jama* 2013;310(16):1683–91.
11. Meng J, Hu M, Lai Z, et al. Levosimendan Versus Dobutamine in Myocardial Injury



Patients with Septic Shock: A randomised Controlled Trial. *Med Sci Monit* 2016;22:1486-96.

12. Belletti A, Castro ML, Silveti S, et al. The Effect of inotropes and vasopressors on mortality: a meta-analysis of randomised clinical trials. *Br J Anaesth* 2015;115(5):656–75.

VANISH

Gordon AC, Mason AJ, Thirunavukkarasu N, Perkins GD, Cecconi M, Cepkova M, et al. Effect of Early Vasopressin vs noradrenaline on Kidney Failure in Patients With Septic Shock: The VANISH randomised Clinical Trial. JAMA. 2016;316(5):509–18.

Introduction

The role of vasopressin infusion in the management of septic shock has yet to be fully elucidated. The 2012 surviving sepsis guidelines provide ungraded recommendations that vasopressin can be used at a dose of 0.03 U/min in the setting of refractory hypotension despite noradrenaline treatment or as a catecholamine sparing agent, but recommends vasopressin should not be used as the initial vasopressor of choice.¹ These guidelines reflect conventional thinking on the physiology of endogenous vasopressin in shock. Vasopressin levels may be elevated in the early phase of shock and fall with increased duration of shock, ultimately resulting in a vasopressin deficient state.^{2,3} Plasma vasopressin levels are corrected by vasopressin infusions, reinforcing that patients are in a deficient state rather than demonstrating increased vasopressin catabolism.^{3,4}

These findings have prompted investigations into the role of vasopressin in septic shock. The biggest trial to date has been the VASST study which compared vasopressin with noradrenaline.⁴ Findings from this trial have generated hypotheses about how vasopressin may benefit patients in septic shock. An a priori subgroup analysis found patients with less severe shock had a lower mortality when treated with vasopressin, while post hoc analysis demonstrated a trend towards less renal failure. In addition, vasopressin was associated reduced mortality when steroids were administered in conjunction with vasopressin.⁴⁻⁶ The VANISH trial investigated the effect of early vasopressin on renal outcomes and also the effect of vasopressin and steroids on mortality.

Study synopsis

This trial hypothesised the use of high dose vasopressin in patients with early septic shock would improve a number of renal outcomes when compared to the use of noradrenaline. To assess the interaction between steroids and vasopressin, a 2x2 factorial design was chosen for this randomised, double-blind trial.

VANISH was conducted in 18 UK ICUs. Patients aged 16 years or over were eligible if they had sepsis requiring vasopressor support. Patients had to be recruited within 6 hours of onset of shock. Sepsis was defined as a known or suspected infection with ≥ 2 of the SIRS criteria being fulfilled. Patients were required to have received adequate fluid resuscitation, although no minimum volume was set. Exclusion criteria included previous



catecholamine use during the ICU stay, steroid dependence, end stage renal failure, vascular pathology such as mesenteric ischaemia or Raynaud's phenomenon or a lack of commitment to full treatment.

Due to the 2x2 factorial nature of the trial design, patients could be randomly assigned to one of four treatment groups; vasopressin and placebo, vasopressin and steroids, noradrenaline and placebo or noradrenaline and steroids. Randomisation was conducted using block sizes of 4 or 8 and was stratified based on treatment centre.

The first therapeutic component consisted of either vasopressin titrated to a maximum of 0.06 U/min or noradrenaline titrated to a maximum of 12 µg/min with a target mean arterial pressure (MAP) of 65 to 75 mm Hg. Patients could receive open label catecholamines as the study drug was commenced, up to a maximum of six hours. As the patient improved open label catecholamines were weaned first. In instances of recurrent hypotension occurring in the first 24 hours after cessation of the study drug, it was recommenced. Beyond 24 hours, open label catecholamines were used.

Only once vasopressin or noradrenaline infusions were at maximal doses was the second drug added (i.e. hydrocortisone or placebo). Patients then received either hydrocortisone 50 mg 6 hourly or identical placebo for five days. The dose was reduced over six days until it was stopped. Once this second drug was given additional open label catecholamines could be used if the target MAP was not achieved.

Kidney failure-free days, defined as the number of days with a Acute Kidney Injury Network (AKIN) score of less than 3 in the first 28 days was the primary outcome measure. This was reported in two ways to reflect the competing risk of death: (1) the proportion of patients who survived to day 28 and who never developed AKIN stage 3 kidney failure and (2) the median number of days alive and free from kidney failure for those that developed kidney failure, died or both. Secondary outcomes included duration of kidney failure, rates of renal replacement therapy (RRT), organ failure free days and mortality.

Assuming a 30% to 50% incidence of AKIN stage 3 kidney injury, and allowing for attrition, 412 patients were required to detect a 20% to 25% relative reduction in the primary outcome measure with a 80% power at the 5% significance level. A modified intention-to-treat analysis was used. As not all patients would progress to receive either placebo or hydrocortisone, as-treated and per-protocol analyses were used. In the as-treated analysis, patients who did not require the second study drug were grouped with patients who had received placebo. Those who crossed over between groups, for example due to open table use of hydrocortisone or vasopressin, were reallocated. The per-protocol analysis excluded all those who had not received the allocated study drug as intended. Regression analysis was used to test for interaction between vasopressin



and hydrocortisone.

A total of 2,213 patients were screened and 1,792 patients were excluded, the majority (1,236 patients) as they fell outside the 6 hour recruitment window. A total of 421 patients were randomised. Analysis is presented for 408 patients (7 were excluded prior to administration of the study drug as they had met exclusion criteria, a further 5 patients withdrew consent and one patient consented but subsequently refused ongoing participation).

The groups were well balanced at baseline, with a typical patient being a Caucasian male in their mid 60s. The median APACHE II score was 24 and 58% of patients required mechanical ventilation at the time of enrolment. The median serum creatinine was 1.38 mg/dL (122 µmol/L), at baseline, with 21% of patients meeting AKIN stage 3 kidney failure criteria. The median time from onset of shock to initiation of study drug was 3.5 hours.

At baseline, 76% of patients were receiving open label noradrenaline at a median dose of 0.16 µg/kg/min. The median volume of fluids administered prior to initiation of the study drug was 1,134 mL, and was similar across all groups. The mean volume of fluid administered from randomisation to the end of the first calendar day was 2,889 ± 3,813 mL vs 2,805 ± 2,455, in the vasopressin and noradrenaline groups, respectively. There was no significant difference in the volume of fluid administered or total fluid balance in any of the first seven days when either vasopressin was compared to noradrenaline or hydrocortisone was compared to placebo. On day one, the total dose of noradrenaline (both study drug and open label) was approximately 0.3 µg/kg/min in the noradrenaline group and 0.15 µg/kg/min in the vasopressin group. The total dose of noradrenaline was similar during the first seven days in the vasopressin and noradrenaline groups. The lowest MAP in the vasopressin and noradrenaline groups from days 1 to 7 ranged from approximately 60 mm Hg to 70 mm Hg.

There was no difference in the proportion of patients who survived to day 28 and who never developed AKIN stage 3 kidney failure; 57.0% in the vasopressin group compared to 59.2% in the noradrenaline group (absolute difference, -2.3%; 95% CI, -13.0% to 8.5%; P=0.88). There was no difference in the median number of days alive and free from kidney failure for those that developed kidney failure, died or both; median 9 days (IQR 1 to 24) in the vasopressin group compared to 13 (IQR 1 to 25) in the noradrenaline group (absolute difference, -4 days; 95% CI, -11 to 5).

The use of RRT was lower in the vasopressin group compared to the noradrenaline group; 25.4% vs 35.3% (OR, 0.40; 95% CI, 0.20 to 0.73). 28 day mortality rates were similar between the two groups; vasopressin (30.9%) and noradrenaline (27.5%) (absolute difference, 3.4%; 95% CI, -5.4% to 12.3%). Vasopressin and noradrenaline



shared a similar safety profile.

The as-treated (n=408) and per-protocol analysis (n=294) demonstrated hydrocortisone resulted in no differences in renal failure, need for RRT or mortality. No interaction between vasopressin and hydrocortisone was found in relation to 28 day mortality (P=0.98).

Study critique

This large trial involving 408 patients was well conducted and has furthered our knowledge in the role of vasopressin in the management of early septic shock. VANISH has many strengths. Patients were randomised and had their study drug commenced on average 3.5 hours after the onset of shock. This compares similarly to the 2.5 hours taken to recruit patients into the ProMISE trial investigating early, goal-directed therapy.⁷

Post hoc analysis of the VASST trial suggested an interaction between vasopressin and hydrocortisone resulted in a reduction in 28 day mortality.⁶ The manner of administration of hydrocortisone in this trial is likely to reflect current clinical practice and surviving sepsis guidelines, with administration only when vasopressors were used at higher doses (vasopressin and noradrenaline at 0.06 U/min and 12 µg/min, respectively).¹ To account for some patients not receiving steroids, an as-treated and per-protocol analysis were performed, reinforcing the strength of trial design.

Some minor points warrant discussion in relation to the renal outcomes used. The choice of kidney failure-free days was defined using two measures (described above). Although the definition of the primary outcome measure is complex, it is difficult to see how an alternative primary outcome measure would have been better. For example, use of RRT would also suffered from the challenges of competing risk of death and RRT is not initiated or delivered in a consistent way between clinicians.⁸ It appears appropriate the trial design factored the competing risk of death as the mortality rate in the vasopressin group was 30.9%. Furthermore, the use of AKIN criteria provides an objective measure of renal dysfunction.^{9,10}

The post hoc analysis from the VASST study demonstrated patients in the “risk” category of the RIFLE criteria were those deriving benefit from vasopressin; less went on to develop “failure” or “loss” levels of kidney injury.^{5,11} There was no benefit seen in patients without kidney injury.⁵ In the VANISH trial all patients with septic shock who required vasopressors were recruited, not just those who fulfilled the “risk” criteria. Therefore, a subtly different group was studied. However, as smaller studies have also demonstrated beneficial effects of vasopressin on renal indices it seems reasonable to have recruited patients with early sepsis who are inherently predisposed to renal dysfunction.^{12,13}



The primary outcome measure was kidney failure-free days in the first 28 days, as defined as AKIN stage 3. The post hoc analysis of the VASST trial demonstrated a reduction in the number of patients who progressed to fulfill the RIFLE criteria for “failure” or “loss”.⁵ For patients to meet the definition of “loss”, they are required to have > 4 weeks of renal dysfunction (table 7).¹¹ It is notable, however, this post hoc analysis only followed patients for 28 days.⁵ Therefore, despite the 28 day follow up and move to AKIN criteria, the primary outcome measure in the VANISH trial would still measure the same level of renal dysfunction as the post hoc analysis of the VASST study.^{5,9-11}

| RIFLE criteria ¹¹ | AKIN criteria ⁹ |
|---|--|
| Risk <ul style="list-style-type: none"> Increase in serum creatinine \times 1.5 or GFR[#] decrease > 25% or UO* < 0.5 ml/kg/hour \times 6 hours | 1 <ul style="list-style-type: none"> Increase in serum creatinine \times 1.5 to 2-fold or Increase in serum creatinine \geq 0.3 mg/dl (26.4 μmol/l) or UO < 0.5 ml/kg/hour for > 6 hours |
| Injury <ul style="list-style-type: none"> Increase in serum creatinine \times 2 or GFR decrease > 50% or UO < 0.5 ml/kg/hour \times 12 hours | 2 <ul style="list-style-type: none"> Increase in serum creatinine \times 2 to 3-fold or UO < 0.5 ml/kg/hour for > 12 hours |
| Failure <ul style="list-style-type: none"> Increase in serum creatinine \times 3 or GFR decrease > 75% or Serum creatinine \geq 4.0 mg/dl (350 μmol/l) with an acute rise > 0.5 mg/dl (44 μmol/l) or UO < 0.3 ml/kg/hour \times 24 hours or anuria \times 12 hours | 3 <ul style="list-style-type: none"> Increase in serum creatinine to > 3-fold or Serum creatinine \geq 4.0 mg/dl (354 μmol/l) with an acute rise > 0.5 mg/dl (44 μmol/l) or UO < 0.3 ml/kg/hour for 24 hours or anuria \times 12 hours |
| Loss <ul style="list-style-type: none"> complete loss of kidney function > 4 weeks | N/A |
| End-stage <ul style="list-style-type: none"> End-stage kidney disease > 3 months | N/A |

Table 7: Comparison of RIFLE and AKIN criteria

glomerular filtration rate, * Urine output

Despite similar rates of AKIN stage 3 renal dysfunction, the rate of RRT was less in the vasopressin group. As the implementation of RRT was at the discretion of the treating clinicians, there could be a number of potential explanations for this. Vasopressin use is associated with improved urine output and lower creatinine.^{12,13} In addition, vasopressin

has a noradrenaline sparing effect, and patients in the noradrenaline group may have been placed on RRT in an effort to reduce catecholamine doses.¹⁴ The investigators postulate this reduction in RRT may represent a patient-centred outcome; however, the duration of RRT in both groups was very short {3 (IQR 2 to 7) days in the vasopressin group and 3 (IQR 2 to 8) days in the noradrenaline group}.

Overall, this was an excellent trial which has answered many of the questions the VASST trial generated regarding vasopressin use in sepsis. The subtle differences in the patient cohort studied and renal outcome measured are important to consider.

Where this sits in the body of evidence

A small study compared 19 patients with septic shock to 12 patients with cardiogenic shock, all of whom were catecholamine-dependant. The mean systolic arterial pressure and cardiac output were 98 mm Hg and 6.8 L/min compared with 99 mm Hg and 3.5 L/min in the septic shock and cardiogenic shock groups, respectively. The mean plasma vasopressin level was 3.1 ± 1.0 pg/mL in the septic shock group compared to 22.7 ± 2.2 pg/mL in the cardiogenic shock group ($P < 0.001$). The addition of vasopressin to the septic shock group resulted in an increase in the mean systolic blood pressure from 92 mm Hg to 146 mm Hg ($P < 0.001$) and an increase in the systemic vascular resistance from 644 to 1187 dyne.s/cm⁵ ($P < 0.001$).³

The VASST trial was the first study to look at the effects of vasopressin on mortality. This multi-centre, randomised, double-blind trial enrolled patients with septic shock (with shock being defined as a requirement for at least 5 µg/min of noradrenaline despite adequate fluid resuscitation) and at least one new organ dysfunction. Patients were randomised to receive either fixed dose vasopressin at 0.03 U/min or noradrenaline at 15 µg/min. Open label vasopressors were titrated to achieve a target MAP of 65 - 75 mm Hg. This study recruited the desired number of patients with 778 patients included in the final analysis. However, the observed mortality of 39.3% in the noradrenaline group was considerably less than the 60% predicted mortality. There was no difference in the primary endpoint of 28 day mortality (adjusted odds ratio, 0.88; 95% CI, 0.62 to 1.26; $P = 0.26$). There was no difference in 90 day mortality or rates of organ dysfunction.⁴

A priori subgroup analysis of patients within the VASST trial demonstrated those suffering from less severe shock (requiring 5-14 µg/min noradrenaline) had improved 28 day mortality when treated with vasopressin (relative risk, 0.75; 95% CI, 0.55 to 1.01; $P = 0.05$). This benefit remained at 90 days ($P = 0.04$). However, the test for interaction between allocation to vasopressin and less severe shock was not significant ($P = 0.10$). There was no difference in mortality between vasopressin and noradrenaline treatment groups in those suffering from severe shock (requiring ≥ 15 µg/min noradrenaline).⁴

Post hoc analysis of patients from the VASST trial looked at the effects of vasopressin on

renal outcomes. Of the 778 patients in the original trial, 106 fell into the RIFLE “risk” category. Over the 28 day study period, 20.8% (n=11) of those treated with vasopressin went on to develop “failure” or “loss”, compared to 39.6% (n = 21) in the noradrenaline group (P=0.03). The number of patients who required RRT was also lower in the vasopressin group (P=0.02). Due to multiple testing performed in this study, a P-value of 0.01 was considered statistically significant.⁵

Another post hoc analysis of data from the VASST trial examined the interaction between steroids and vasopressin. In patients with septic shock treated with steroids, those who received vasopressin (n=296) had a 28 day mortality rate of 35.9% compared 44.7% in those who received noradrenaline (n=293) (P=0.03). In the group of patients who did not require steroids, vasopressin (n=101) was associated with a higher mortality, 33.7%, compared to those those who received noradrenaline (n=89), 21.3%, (P=0.06). There was a significant interaction between steroids and vasopressin (P=0.008).⁶

A randomised controlled trial compared two doses of 40 units of vasopressin with two doses of 1 mg of adrenaline in 1,186 patients with out-of-hospital cardiac arrest. There was no difference between vasopressin and adrenaline in the primary endpoint of survival-to-hospital admission in patients with ventricular fibrillation (46.2% vs 43.0%; P=0.48) or pulseless electrical activity (33.7% vs 30.5%; P=0.65). However, in those with asystole, 29.0% of those treated with vasopressin survived to hospital admission, compared to 20.3% of those treated with adrenaline (P=0.02).¹⁵

Should we routinely consider vasopressin for the management of septic shock?

Possibly. Both VASST and VANISH point towards some benefit in renal outcomes with vasopressin, with no indication of harm.

References

1. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013 Feb;41(2):580–637.
2. Sharshar T, Blanchard A, Paillard M, Raphael JC, Gajdos P, Annane D. Circulating vasopressin levels in septic shock. *Crit Care Med*. 2003 Jun;31(6):1752–8.
3. Landry DW, Levin HR, Gallant EM, Ashton RC, Seo S, D’Alessandro D, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation*. 1997 Mar 4;95(5):1122–5.
4. Russell JA, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, et al. Vasopressin versus noradrenaline infusion in patients with septic shock. *N Engl J Med*. 2008 Feb 28;358(9):877–87.



5. Gordon AC, Russell JA, Walley KR, Singer J, Ayers D, Storms MM, et al. The effects of vasopressin on acute kidney injury in septic shock. *Intensive Care Med.* 2010 Jan;36(1):83–91.
6. Russell JA, Walley KR, Gordon AC, Cooper DJ, Hébert PC, Singer J, et al. Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. *Crit Care Med.* 2009 Mar;37(3):811–8.
7. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of Early, Goal-Directed Resuscitation for Septic Shock. *New England Journal of Medicine.* 2015 Apr 2;372(14):1301–11.
8. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, et al. Continuous renal replacement therapy: A worldwide practice survey. *Intensive Care Med.* 2007 Sep 1;33(9):1563–70.
9. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Critical Care.* 2007;11:R31.
10. Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. *Clin Kidney J.* 2013 Feb 1;6(1):8–14.
11. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Critical Care.* 2004;8:R204.
12. Lauzier F, Lévy B, Lamarre P, Lesur O. Vasopressin or noradrenaline in early hyperdynamic septic shock: a randomised clinical trial. *Intensive Care Med.* 2006 Nov;32(11):1782–9.
13. Patel BM, Chittock DR, Russell JA, Walley KR. Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology.* 2002 Mar;96(3):576–82.
14. Combes A, Bréchet N, Amour J, Cozic N, Lebreton G, Guidon C, et al. Early High-Volume Hemofiltration versus Standard Care for Post-Cardiac Surgery Shock. The HEROICS Study. *Am J Respir Crit Care Med.* 2015 Jul 13;192(10):1179–90.
15. Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH. A Comparison of Vasopressin and Epinephrine for Out-of-Hospital Cardiopulmonary Resuscitation. *New England Journal of Medicine.* 2004 Jan 8;350(2):105–13.



CLASSIC

Hjortrup PB, Haase N, Bundgaard H, Thomsen SL, Winding R, Pettilä V, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multi-centre feasibility trial. *Intensive Care Med* 2016;42(11):1695-1705

Introduction

Intravenous fluid therapy traces its origins back to the cholera epidemics of the early 19th century, when Dr Latta famously recorded the restorative effects of fluid resuscitation in Edinburgh in 1832.¹ 200 years ago the volume to be administered was titrated against the strength of the pulse and clinical state of the patient. However, with the increasing recognition of the harms associated with fluid overload, and a lack of sensitivity of any clinical method to accurately determine volaemic status, this has proven less acceptable today.

Modern fluid research is a curious field, where attention has focused on the intricacies of which fluids to give, how much to give and how to trigger starting and stopping administration, but with little deliberation of the paradigm of whether we should actually give any fluid in the first place. Despite two centuries of fluid therapy, the biology of this intervention remains largely unknown.² Whether patients not in fluid losing states should receive fluids is now being seriously questioned.³ Only 50% of critically ill patients are fluid responsive, whereby stroke volume increases with a fluid bolus.⁴ In addition, administered crystalloids largely leave the intravascular space within 60 minutes,⁴ with any circulatory effect also being short lived.⁵ The colloid fallacy had been convincingly challenged with both clinical trial data and an improved understanding of microvascular fluid dynamics. Whether we should administer fluids to shocked patients without fluid losing states has never been formally investigated.

The best evidence for the effectiveness of fluid therapy in sepsis comes from the FEAST trial, comparing fluid resuscitation with saline or albumin with no fluid therapy in critically ill African children.⁶ There was a clear mortality benefit with the avoidance of fluid therapy. However, the unique population studied deserves comment – most patients were very young and suffering from malaria, where IV fluid could potentially lower haematocrit further, and the study was undertaken in a resource-poor environment. Despite this, FEAST is a fascinating study which serves as a clear impetus for urgent research in this area.

The other major area of relevance to this discussion is the early goal-directed therapy field. The first major trial was a small single-centre study from Detroit, by Emanuele Rivers in 2001, demonstrating a large mortality benefit with the use of early goal-directed therapy, as guided by a central venous catheter capable of directly measuring



central venous oxygenation (ScvO₂).⁷ The interventions applied included the use of liberal fluids, dobutamine, red cell transfusion, and sedation with mechanical ventilation if the ScvO₂ remained low. Widely heralded and promoted, despite being a single-centre study without replication, and consisting of numerous goals which themselves were not evidence-based, this study influenced practice over the next several years.

In 2014/15, three follow up trials to the original goal-directed study found no difference between contemporary usual care and the more resource-intensive early goal-directed therapy in septic shock.⁸⁻¹⁰ Of note, patients in the usual care groups received much lower amounts of fluid than those in the control arm of the original Rivers trial, confirming a move away from liberal fluid use in modern sepsis resuscitation. Against this background, the CLASSIC trial¹¹ from Scandinavia, sought to determine if a fluid resuscitation volume trial was feasible in critically ill patients with septic shock.

Study synopsis

The CLASSIC trial was an investigator-initiated phase II, multi-centre, stratified, parallel group randomised trial comparing restrictive fluid resuscitation with standard care in adults with septic shock. Eligible patients were those with septic shock, in the ICU, having received at least 30 ml/kg of fluid within the past 6 hours and requiring noradrenaline to maintain the circulation. Exclusion criteria included renal replacement therapy, hyperkalaemia, plasma creatinine > 350 µmol/L, severe hypoxaemia, life-threatening bleeding, acute burn injury, lack of commitment to full life support and absence of consent.

A mean arterial pressure (MAP) of 65 mm Hg was maintained in both groups with noradrenaline, with the indications for fluid resuscitation differing. The restrictive group could receive fluid boluses of 250 to 500 ml if they were hyperlactaemic (> 4 mmol/L), had a MAP less than 50 mm Hg, mottling below the kneecap, or were oliguric in the first 2 hours after randomisation (urinary output < 0.1 mL/kg/hr). This could be repeated if hypoperfusion persisted. The standard care group could receive repeated fluid therapy as long as haemodynamic measures continued to improve. Isotonic crystalloid solution, either 0.9% saline or Ringer's solution, was used for fluid resuscitation, with colloid therapy not permitted.

The primary outcome measure was the total volume of resuscitation fluid within the first 5 days after randomisation. Secondary outcome measures included total fluid administered and total fluid balance, at both day 5 within ICU and for total ICU stay, number of patients with fluid violations and rates of serious adverse reactions. Exploratory outcomes included various patient-centered outcomes such as death, duration free from organ-support, ischaemic events and kidney injury.

Based on data from the 6S study,¹² 151 patients were required to demonstrate a 1.7 L



between group difference in fluid resuscitation volumes at day 5, with 80% power at the 5% significance level. An intention-to-treat analysis was used, with adjustment for sites recruiting less than 10 patients. As a second outcome, the amount of resuscitation fluid given after randomisation during the entire ICU stay, was changed to a co-primary outcome after the collection of all data, and before analyses was undertaken, the primary outcomes were corrected for multiple testing. Per-protocol sensitivity analyses were also undertaken.

In 9 ICUs in Denmark and Finland, 203 patients were screened and 153 randomised in a 1:1 fashion to each group. Allocation was performed via a centralised, web-based system in permuted blocks of 2 to 4, stratified for centre, with the study statistician blinded to group assignment. Two patients withdrew consent, leaving 76 patients in the restrictive group and 75 in the standard care group.

The groups were largely similar, having a typical ICU study demographic profile of being male (65%), and approximately 70 years of age. Most patients had either a respiratory or abdominal source of sepsis, which were unevenly distributed between groups. Slightly more patients came from operating theatres (~37%) or general wards (~37%), than the emergency department (~23%). Equal numbers of patients received mechanical ventilation (56%). More patients in the restrictive group had acute kidney injury at baseline (51% vs 38%). The restrictive group received a median of 4,200 ml (IQR, 3,461 to 6,700) and the standard group 4,790 ml (3,232 to 6,847) at study entry.

Patients underwent randomisation within a median of 4.5 (2.0 to 8.5) hours, in the restrictive group and 4.0 (1.5 to 6.5) hours in the standard care group, of admission to ICU, with both groups having been in hospital for a median of 1 day. SOFA scores were similar at 10, and median lactate values were also comparable (restrictive 3.0 mmol/L vs standard group 2.5 mmol/L).

The co-primary outcomes were achieved, with a between group difference of 1.2 L (95% CI, -2.0 to -0.4; $P < 0.001$) for the ICU-delivered resuscitation volume at day 5 and 1.4 L (95% CI, 2.4 to 0.4; $P < 0.001$) for the total ICU stay. These findings were consistent across sensitivity analyses. There was no difference in total fluid volume at day 5 or for the ICU stay. Although one third of the restrictive fluid group had a protocol violation, there was no difference in serious adverse events. Similarly, there was no difference in the exploratory endpoints, including death at 90 days (restrictive group 33% vs standard care 41%; OR, 0.71, 95% CI, 0.36 to 1.40; $P=0.31$), ischaemic events (4% vs 12%; OR, 0.32, 95% CI, 0.08 to 1.27; $P=0.11$) and worsening of acute kidney injury (37% vs 54%; OR, 0.46, 0.23 to 0.92; $P=0.03$).

Study critique

Despite being a phase II trial, the CLASSIC trial is the first to produce prospective,



randomised data on the age old question of how much fluid should we give our patients with haemodynamic compromise. The study has many positive features, which bodes well for the phase III trial.

The question is not only pertinent, but has been narrowed to post initial resuscitation fluid volumes, avoiding a heterogenous data capture. The volume administered during the prior resuscitation phase were comparable to volumes administered at 6 hours in all four of the early goal-directed therapy studies. Two recent prominent studies comparing fluid resuscitation in the ICU with a starch or saline,^{12,13} had similar times to randomisation and total volume administered at the end of the ICU stay. Day 5 values were not an endpoint in either of these trials.

The criteria required for the administration of further resuscitation fluid were specified and severe, which had the effect of identifying a population with genuine circulatory disturbance and increased the likelihood of recognising a signal, should one exist. The prior fluid resuscitation studies in ICU left the requirement for fluid to the judgement of the treating physician, which was appropriate as they were studies of fluid type rather than volume.

The power calculation was based on data from the 6S trial, work which the group had previously undertaken, meaning the data was specific for the population they intended to study.

As with any critical care study, there were a number of protocol violations, which largely reflects the complexity of running such a trial and should help inform the design of the phase III trial. A clear confounder would have been the use of colloids, given their slightly increased, although short-lived, plasma expanding volumes. As they are no longer recommended for use in the critically ill, it was not surprising that no synthetic colloid was administered in the study; however, over 20% of each group received albumin. Some caveats to mention include the use of a protocolised standard care group, rather than genuine “wildtype” standard care, the exclusion of patients requiring renal replacement therapy, and the lack of microbiological data, a criticism common of most sepsis trials.

Where this sits in the body of evidence

Maitland et al performed a stratified (severe hypotension or not), multi-centre, randomised control trial, in a resource-limited setting in sub-Saharan Africa, comparing a fluid bolus (20 to 40 ml of 5% albumin or 0.9% saline) with no fluid bolus at admission to hospital in 3,141 children with febrile illness and impaired perfusion.⁶ They found fluid bolus therapy was associated with a higher mortality at 48 hours (albumin 10.6%, saline 10.5%, no bolus 7.3%; relative risk bolus therapy versus no bolus 1.45, 95% CI, 1.13 to 1.86, P=0.003), and 28 days (12.2%, 12.0% & 8.7%, respectively; RR bolus therapy versus



no bolus $p=0.004$), with similar incidences of pulmonary oedema, increased intra-cranial pressure (2.6%, 2.2% versus 1.7% $P=0.17$), and neurological sequela in the three groups ($P=0.92$).

Rivers and colleagues randomly assigned 263 patients with severe sepsis or septic shock to six hours of early goal-directed therapy, guided by ScvO₂ monitoring, or standard care in the emergency department prior to ICU admission.⁷ The interventions included fluids, vasoactive agents, red cells, and sedation with invasive mechanical ventilation. Patients in the early goal-directed therapy group received significantly more fluid within the first 6 hours ($4,981\pm 2,984$ vs $3,499\pm 2,438$ ml; $P<0.001$), less fluid between hours 7 and 72 ($8,625\pm 5,162$ vs $10,602\pm 6,216$ ml; $P=0.01$), with no overall difference at 72 hours ($13,443\pm 6,390$ vs $13,358\pm 7,729$ ml). Early goal-directed therapy resulted in a large in-hospital mortality benefit (30.5% vs 46.5%; RR 0.58, 95% CI, 0.38 to 0.87; $P=0.009$), an effect which was maintained at 28 and 60 days.

The ProCESS trial was the first of three contemporary studies examining early goal-directed therapy in septic shock.⁸ 1,341 patients were randomised to protocol-based EGDT ($n=439$), protocol-based standard therapy ($n=446$) or usual care ($n=456$). The groups separated significantly with regard to fluids (2.8 l vs 3.3 l vs 2.3 l, respectively; $P<0.001$). There was no difference in the primary outcome of 60 day mortality; protocol-based EGDT 21.0%, protocol-based standard therapy 18.2% and usual care 18.9%, or mortality at 90 days or 1 year.

The second trial in this triumvirate of studies was the ANZICS ARISE trial, comparing EGDT with usual care in 1,600 patients with early septic shock.⁹ Again, patients in the EGDT received more interventions within the first 6 hours: fluids ($1,964\pm 1,415$ ml vs $1,713\pm 1,401$ ml), vasopressors (66.6% vs 57.8%), red-cell transfusions (13.6% vs 7.0%), and dobutamine (15.4% vs 2.6%) ($P<0.001$ for all comparisons). There was no difference in the primary outcome of day 90 mortality (18.6% vs 18.8%; difference -0.3%, 95% CI -4.1 to 3.6; $P=0.90$) or other patient-centered outcomes.

The third modern EGDT was the UK ProMISe trial in 1,260 patients with early septic shock. As before, the EGDT group ($n=630$) received more interventions, including total fluids, EGDT group 2,000 ml (1,150 to 3,000) vs 1,784 ml (1,075 to 2,775), within the first 6 hours.¹⁰ Although there was no difference in the primary outcome of 90 day mortality (EGDT group 29.5% vs usual care 29.2%; RR, 1.01; 95% CI, 0.85 to 1.20; $P=0.90$), several secondary outcomes were significantly worse with EGDT, including mean SOFA score at 6 hours (6.4 ± 3.8 vs 5.6 ± 3.8), proportion requiring advanced circulatory support (37% vs 30.9%) and length of ICU stay (2.6 vs 2.2). The probability that EGDT was cost-effective was less than 20%.

Despite three recent high-quality RCTs demonstrating no benefit with EGDT, a host of



meta analyses published from 2015 onwards, each including between 5 and 10 RCTs, reported widely differing results, ranging from harm to benefit.^{14–18}

The Fluids and Catheters Treatment Trials (FACTT) compared a conservative with liberal fluid strategy in 1,000 patients with acute lung injury.¹⁹ Haemodynamic management was achieved with a complex protocol. Depending on several variables (central venous pressure or pulmonary artery wedge pressure, urinary output and mean arterial pressure), various interventions including fluids, diuretics, or dobutamine, were administered to achieve target goals. At day 7, the conservative group achieved a net neutral fluid balance (-136 ± 491 ml) in comparison with a net $+ 6,992\pm 502$ ml balance in the liberal arm. There was no statistically significant difference in the primary outcome of mortality at day 60 (conservative group 25.5% vs liberal group 28.4%; 95% CI, -2.6 to 8.4% , $P=0.30$), although there were more ventilator-free days with the conservative approach (14.6 ± 0.5 vs 12.1 ± 0.5 ; $P<0.001$). In a very small follow-up study including just 10% of the original cohort, the conservative approach was associated with more neuropsychological complications.²⁰

On the basis of this trial, should we restrict the volume of fluid given to patients with septic shock who have already received fluid resuscitation?

No. This is a pilot trial which is not powered for patient-centered outcomes. The findings of the subsequent phase III trial are eagerly awaited. For those already practicing restrictive fluid therapy, this study supports this approach, but is not definitive enough to change practice.

References

1. MALIGNANT CHOLERA. Orig Publ Vol 2 Issue 457 1832;18(457):274–80.
2. Hilton AK, Bellomo R. A critique of fluid bolus resuscitation in severe sepsis. Crit Care 2012;16(1):302.
3. Hilton AK, Bellomo R. Totem and Taboo: Fluids in sepsis. Crit Care 2011;15(3):164.
4. Marik P, Bellomo R. A rational approach to fluid therapy in sepsis. Br J Anaesth 2015;aev349.
5. Glassford NJ, Eastwood GM, Bellomo R. Physiological changes after fluid bolus therapy in sepsis: a systematic review of contemporary data. Crit Care 2014;18(6):1.
6. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech, et al. Mortality after fluid bolus in African children with sepsis. N Engl J Med 2011;364(26):2483-95.
7. Rivers E, Nguyen B, Havstad S, et al. Early Goal-Directed Therapy in the Treatment of



Severe Sepsis and Septic Shock. *N Engl J Med* 2001;345(19):1368–77.

8. Investigators P. A randomised trial of protocol-based care for early septic shock. *N Engl J Med* 2014;2014(370):1683–93.
9. Investigators A, Group ACT. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014;2014(371):1496–506.
10. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015;372(14):1301–11.
11. Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multi-centre feasibility trial. *Intensive Care Med* 2016;42(11):1695–705.
12. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis. *N Engl J Med* 2012;367(2):124–34.
13. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. *N Engl J Med* 2012;367(20):1901–11.
14. Angus DC, Barnato AE, Bell D, et al. A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators. *Intensive Care Med* 2015;41(9):1549–60.
15. Zhang L, Zhu G, Han L, Fu P. Early goal-directed therapy in the management of severe sepsis or septic shock in adults: a meta-analysis of randomised controlled trials. *BMC Med* 2015;13(1):1.
16. Yu H, Chi D, Wang S, Liu B. Effect of early goal-directed therapy on mortality in patients with severe sepsis or septic shock: a meta-analysis of randomised controlled trials. *BMJ Open* [Internet] 2016;6(3). Available from: <http://bmjopen.bmj.com/content/6/3/e008330.abstract>
17. Xu J-Y, Chen Q-H, Liu S-Q, et al. The Effect of Early Goal-Directed Therapy on Outcome in Adult Severe Sepsis and Septic Shock Patients: A Meta-Analysis of randomised Clinical Trials. *Anesth Analg* 2016;123(2):371–81.
18. Chelkeba L, Ahmadi A, Abdollahi M, Najafi A, Mojtahedzadeh M. Early goal-directed therapy reduces mortality in adult patients with severe sepsis and septic shock: Systematic review and meta-analysis. *Indian J Crit Care Med* 2015;19(7):401–11.
19. The National Heart Lung, Blood Institute. Comparison of Two Fluid-Management Strategies in Acute Lung Injury. *N Engl J Med* 2006;354(24):2564–75.
20. Mikkelsen ME, Christie JD, Lanken PN, et al. The Adult Respiratory Distress Syndrome Cognitive Outcomes Study. *Am J Respir Crit Care Med* 2012;185(12):1307–15.



EMPIRICUS

Timsit JF, Azoulay E, Schwebel C, Charles PE, Cornet M, Souweine B, et al. Empirical Micafungin Treatment and Survival Without Invasive Fungal Infection in Adults With ICU-Acquired Sepsis, Candida Colonization, and Multiple Organ Failure The EMPIRICUS randomised Controlled Trial. JAMA 2016;316(15):1555-1564

Introduction

Candida infections are amongst the most common causes of nosocomial blood stream infections, with up to two-thirds of all episodes of candidaemia occurring in the intensive care unit.¹ Critical care patients with candida bloodstream infections have prolonged intensive care and hospital length of stay.² Furthermore mortality associated with invasive candida infections may be as high as 30% to 50%.^{2,3} Prompt treatment and source control improves outcomes.^{4,5} However, therapy may be delayed because of the relative insensitivity of blood cultures and the time needed for blood cultures to yield growth.¹ Although other diagnostic tests are available, their use in routine practice is limited. As a result empiric prophylaxis of anti-fungals in selected patients has been investigated in both surgical and general intensive care populations.⁶⁻¹¹ However although results for prophylaxis in surgical patients is promising,⁶⁻⁸ the results in the general critical care population are less encouraging.⁹⁻¹¹ Nevertheless, a recent meta-analysis suggested that prophylaxis may be beneficial although the quality of the evidence was generally poor.¹² Prophylaxis in selected critically ill patients is also recommended in international guidelines.¹ Therefore, further evidence on this potentially lifesaving intervention is important. The EMPIRICUS trial investigated the effect of micafungin in a selected critical care population.

Study synopsis

This was a multi-centre, randomised double-blind trial performed in 19 intensive care units in France. The aim was to compare a 14 day empirical course of micafungin with placebo on the 28 day survival without invasive fungal infection in critically ill patients with suspected invasive candidiasis.

Adult patients who were mechanically ventilated for at least 5 days, with one or more other organ failure, and new intensive care-acquired sepsis of unknown origin, who had previously broad spectrum antibiotic cover for more than four days in the previous week, had an arterial or central line insitu and had candida species colonisation at one or more sites, were eligible for enrolment. Patients were excluded if they were neutropenic (neutrophils $<500/\text{mm}^3$), had a previous bone marrow or solid organ transplant, had ongoing immunosuppressant therapy or had been treated in the previous seven days with an echinocandin at any stage or any other anti-fungal for more than 3 days.



Randomisation was performed via a web based programme produced an independent statistician. Patients were randomised to either micafungin 100 mg for 14 days or placebo. The study drug was prepared by research pharmacists in opaque bags to maintain blinding. After randomisation patients had blood cultures performed prior to administration of the study drug. Fundoscopy, echocardiography and sampling of potential infected sites for the diagnosis of invasive fungal infection was also performed. If a subsequent invasive candidiasis was diagnosed or another anti-fungal treatment was commenced then the study drug was withdrawn and anti-fungal treatment administered (as per the treating physicians). The patient remained blinded and was included in the modified intention-to-treat analysis.

The primary end point was 28 day survival free of proven invasive fungal infection using a modification of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Study Group definitions.¹³ Secondary end points included new proven invasive fungal infections, survival at 28 and 90 days, anti-fungal-free survival, ventilator-associated pneumonia rates, SOFA score progression and serum levels of (1-3)- β -D-glucan. There were, a number of secondary analysis planned in pre defined subgroups thought to be at increased risk of fungal infections; medical vs surgical, low vs high SOFA score, low vs high (1-3)- β -D-glucan level, low vs high colonization index, Candida score <3 vs \geq 3.

There were several issues to consider when undertaking the power calculation. These included mortality in the population, the mortality in treated candidaemia, the incidence of invasive candidaemia and the sensitivity of diagnostic tests. To detect a difference of 18% in the primary endpoint with an 80% power at a 0.05 significance level, 235 patients were required. This would result in an increase from 37% of patients free from proven infection in the placebo group to 55% in the micafungin group. It was decided that 260 patients were needed to account for attrition. All patients who received at least one dose of study drug were included in the analysis on an intention-to-treat basis.

518 patients were screened. Of the 258 excluded, 65% did not meet the eligibility criteria, a further 13% were in another study and another 11% had consent problems. Ultimately, 130 patients were randomised to each group. The characteristics in each group were similar, although the micafungin group had proportionally more diabetic patients (34% versus 20%) while the placebo group had more chronic respiratory conditions (26% versus 16%). A typical patient was around 64 years of age, with a median SOFA score of 8 (6 to 11). Patients were mainly medical with acute respiratory failure (40%) and or sepsis (34%). 20% of patients were from cardiac surgery. 56% of patients required inotropes, 33% required dialysis and a quarter were on parenteral nutrition. Only 9% of patients were receiving steroids. Median ICU stay was 10 days (7-16).



Overall 87 patients (68%) in the micafungin group vs 74 patients (60.2%) in the placebo group were alive and free from invasive fungal infection at day 28 (HR, 1.35; 95%CI, 0.87 to 2.08; P=0.18). There were no significant differences in the pre-defined subgroup analyses or when the 12 patients who had invasive fungal infections diagnosed at inclusion were removed. For the secondary outcomes, 12% of the placebo group and 3% of the micafungin group, developed at least 1 new proven invasive fungal infection (P=0.008). Despite this, there were no differences in 28 day survival (70% placebo vs 70% micafungin; P=0.95) or 90 day survival (55% placebo vs 56% micafungin; P=0.90). There were no other significant differences in any other outcome measures. Micafungin was well tolerated with minimal adverse effects in comparison to the placebo.

Study critique

Invasive fungal infections (IFIs) are a frequent complication of critically illness. Critical illness is associated with a host of risk factors predisposing to fungal infections including Candida colonization, severity of illness, exposure to broad spectrum antibiotics, recent major surgery, particularly abdominal surgery, necrotizing pancreatitis, dialysis, parenteral nutrition, corticosteroids, and the use of central venous lines.¹ Proven diagnosis of fungal infections requires either histology or culture which can take time and delay treatment.¹³ As delayed therapy is associated with worsening outcomes,⁴ it is perhaps not surprising that attention has focused on risk factor identification and administration of anti-fungal before microbiological diagnosis.¹

Administration of anti-fungal therapy prior to the definitive microbiological evidence of fungal infection constitutes an untargeted approach. Within this untargeted approach there also exist several different administration strategies. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has recently provided definitions, classifying them into prophylactic, pre-emptive and empiric treatments. They defined prophylaxis as administration in a patient with no evidence of a fungal infection but at risk, pre-emptive as evidence of candidiasis without proof of invasive infection and empiric or fever based where patients have evidence of infection and risk factors, is febrile but with no microbiological diagnosis. These definitions are important as they represent very different patient situations. The Empiricus study therefore is an investigation of empiric treatment.

This trial represents one of the largest investigating the effect of empirical anti-fungal treatment. There are many aspects of this trial that contribute to the quality of the research. The trial was multi-centre and performed across both university-affiliated and non-university hospitals, which adds to the external validity. The central randomisation process was stratified by centre, lessening the influence of any one unit. The study drug was adequately blinded, it was delivered to the majority of patients (there were only 9 patients who did not receive the study drug) and there were no discontinuations. There



was no ambiguity in the primary outcome measure, unlike some previous trials which have included proven and probable infections. Empiricus used only proven infections.^{7,10} The investigators also used an independent adjudication committee for all cases of possible candidiasis before unblinding. These measures reduced the possibility of bias. Data collection was thorough and there were no patients lost to follow-up. Finally, the investigators collated large amount of data related to risk for candidaemia. A subsequent analysis questioned the usefulness of surveillance of candida colonisation. This could have major implications for practice.

There have been multiple trials investigating anti-fungal treatment prior to the actual diagnosis of an infection. The premise of this untargeted treatment is to either prevent infection or treat early when infection is suspected and therefore reduce mortality, as in this trial. The hypothesis of these interventions is surely different. Untargeted anti-fungal trials have been the subject of previous meta-analysis with the results analysed together, but this strategy is suboptimal.¹² The primary outcome is often the development of proven or probable fungal infection, which is appropriate in a trial of prophylaxis but in a trial of empirical therapy where infection is somewhat suspected a more robust patient outcome measure is required, such as mortality. The hypothesis in the Empiricus trial was that micafungin would increase the proportion of patients surviving and free of proven fungal infection. It failed to show this. The results did show some of these critically unwell patients who were suspected of having candida infection had positive initial cultures; therefore, they had early treatment. Additionally, micafungin seemed to reduce the number of diagnoses of further candida infections, although this could also be delayed diagnosis, as diagnostic tests have poor sensitivity. However, it is hard to draw firm conclusions from any of these observations as the trial was not large enough to detect a mortality difference in the patients who had candida from the beginning or those who subsequently developed an infection.

It is clear that patient selection is important in any trial. The prevalence of candida infection in the general intensive care population is still relatively low (0.5%),² therefore, patient selection for anti-fungal therapy is critical. Clearly, the higher the prevalence of a condition in a population, the higher the probability of establishing if a treatment effect exists. The Empiricus trial selected patients with new sepsis who had been in the ICU for a relatively prolonged time, were colonised with candida, ventilated with one other organ dysfunction, had a central or arterial line and had had broad spectrum antibiotics. This is an exclusive group of patients and perhaps explains the 2.5 year recruitment period. The inclusion criteria have been associated with increased risk of fungal infection, although a slight criticism is that the patient could have either a central line or arterial line when the risk appears to be correlated with a central venous lines.¹ Furthermore, over three quarters of patients had a Candida score¹⁵ greater than three and 80% had a colonisation index¹⁶ greater than >0.5, indicating these patient were at higher risk of invasive Candida infections. Yet, the overall rate of infection at 28 days was



around 11%. This was higher than the event rate predicted in the micafungin group and lower than that expected in the placebo, but overall was not greatly different from the event rate expected. Perhaps a population with higher risk, might be worth studying in greater detail.

Several other authors have suggested that better risk prediction is required.¹⁷ As such, the investigators also measured (1-3)- β -D-glucan levels. β -D-glucan is a cell wall constituent of *Candida* and several other fungal species. β -D-glucan levels in intensive care patients have been found to be higher in those with invasive candidaemia than in those without and its detection precedes a microbiologic diagnosis by several days.^{10,13,18} False positives results can be problematic, with elevated levels found in bacteremia, some antibiotics administration, hemodialysis, transfusion of albumin or immunoglobulin amongst others and crucially, fungal colonisation,¹ factors which are all associated with intensive care patients. Nevertheless, a meta analysis¹⁹ has suggested β -D-glucan is useful and it is recommended in the diagnosis of probable infections.¹⁴ Interestingly, in this study β -D-glucan levels were elevated in both micafungin and placebo groups. The levels were unaffected by micafungin therapy. When outcomes were analysed for patients with elevated β -D-glucan levels there was no difference in outcome, suggesting in this population the use of β -D-glucan was not able to guide therapy. In fact, none of the predefined risk factors were associated with better outcomes, although patients with elevated SOFA scores (>8) had a non-significant trend towards better outcome with micafungin therapy.

While the Empiricus trial did not show a benefit of empirical therapy, this is consistent with empirical therapy in two other trials in mixed intensive care patients using fluconazole and caspofungin.^{9,10} There are a few considerations before abandoning empirical treatment on the basis of this trial. Although there was consideration in the design of the trial, the actual diagnosis of invasive fungal infections was based on proven infections. This heavily relies on blood cultures, the overall sensitivity of which for diagnosing invasive candidiasis is roughly 50%.²⁰ In the presence of a candidaemia, blood cultures should be positive, however, negative results can occur in the presence of low-level candidemia, intermittent candidemia, or in deep-seated candidiasis.¹ There is a likelihood that when using proven infections, some diagnosis will be missed. The protocol did not specify the diagnostic procedures to follow for fungal infections. Nor did the protocol state how to manage central lines, which have strongly correlated with infections. Guidelines recommend removal in the case of proven infection.¹⁴ Another confounding factor was the higher incidence of diabetic patients in the micafungin group, which potentially could increase the risk of fungal infections.

This is a complex area to research; power calculations are difficult as risk is generally low and factors for predicting increased risk are generally inadequate and diagnostics are not entirely reliable. Despite limited quality evidence, guidelines¹ generally recommend



therapy in suspected cases, perhaps due to the dire consequences of delayed treatment. Future studies are needed in prophylactic, pre-emptive, and empiric situations.

Where this sits in the body of evidence

In a multi-centre, blinded randomised controlled trial in the USA, 270 intensive care patients with fever despite administration of broad-spectrum antibiotics, a central line in-situ and an APACHE 2 score > 16 were randomised to either intravenous fluconazole, 800 mg daily, or placebo for 2 weeks. The primary outcome was a composite of resolution of fever, absence of invasive fungal infection, absence of toxicity, and no treatment with additional anti-fungal therapy. Only 36% of fluconazole recipients and 38% of placebo recipients had a successful outcome at 28 days (RR, 0.95; 95% CI, 0.69 to 1.32; P=0.78). Invasive candidiasis occurred in 5% of fluconazole recipients and 9% of placebo recipients (RR, 0.57; 95% CI, 0.22 to 1.49).⁹

In a multi-centre, randomised, double-blind, placebo-controlled trial of caspofungin prophylaxis versus placebo, 222 adults who were in the ICU for at least 3 days, were ventilated, received antibiotics, had a central line, and had 1 additional risk factor (parenteral nutrition, dialysis, surgery, pancreatitis, systemic steroids, or other immunosuppressants) were recruited. The primary endpoint was the incidence of proven or probable invasive candidiasis. The incidence of proven/probable invasive candidiasis in the placebo and caspofungin arms was 16.7% and 9.8%, respectively, for prophylaxis (P =0.14). There were no significant differences in the secondary endpoints of mortality, anti-fungal use, or length of stay.¹⁰

In a prospective, randomised, double-blind, placebo-controlled trial in a mixed intensive care unit at a university hospital, 204 patients ventilated for at least 48 hours and who had an expectation to remain ventilated for an additional 72 hours, and who were receiving selective digestive decontamination were randomised to fluconazole 100 mg daily (n=103) or placebo (n=101). Candida infections occurred less frequently in the fluconazole group (5.8%) than in the placebo group (16%; rate ratio 0.35; 95% CI, 0.11 to 0.94) P=0.02. Crude in-hospital mortality was similar in the two groups (39% fluconazole vs 41% placebo).¹¹

In a prospective, randomised, placebo-controlled trial in a tertiary care surgical intensive care unit. 260 critically ill surgical patients with a length of ICU stay of at least 3 days were randomly assigned to receive either enteral fluconazole 400 mg daily or placebo. The primary end point was the time to occurrence of fungal infection during the surgical ICU stay. After adjusting for APACHE III score, days to first dose, and fungal colonisation at enrolment, the risk of fungal infection was reduced by 55% in the fluconazole group (rRR 0.45; 95% CI, 0.21 to 0.98). There was no difference in mortality.⁷

In a double blind multi-centre randomised trial, 241 patients requiring surgery for intra-



abdominal infection were randomised to preemptive anti-fungal with micafungin (100 mg/d) or placebo. 124 patients received placebo and 117 micafungin. The mean (SD) duration of study drug exposure was 8.3 (6.9) days for placebo and 7.7 (6.8) days for micafungin. The incidence of invasive candida infection was 8.9% for placebo and 11.1% for micafungin (difference, 2.24%; 95% CI, -5.52 to 10.20). There was no difference between the arms in median time to infection.¹⁷

In a randomised, prospective, double-blind, placebo-controlled study in two critical care units, 49 patients with recurrent intra-abdominal perforations were randomised to intravenous fluconazole (400 mg per day) or placebo. The primary study end points were the frequency of, and time to, intra-abdominal *Candida* infections. *Candida* was isolated from surveillance cultures during prophylaxis in 15% of the patients in the fluconazole group and in 62% of the patients in the placebo group (RR 0.25; 95% CI, 0.07 to 0.96; P=0.04). *Candida* peritonitis occurred in one of 23 patients (4%) who received fluconazole and in seven of 20 patients (35%) who received placebo (RR, 0.12; 95% CI, 0.02 to 0.93; P=0.02).⁶

Should we use empirical micafungin in critically ill patients with ICU-acquired sepsis, candida colonisation and multi-organ failure?

EMPIRICUS fails to support the role of empirical anti-fungal therapy with micafungin in this population. Current practice should continue to follow local and international guidelines pending the inclusion of this trial's results in updated versions.

References

1. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016; 62(4):e1-e50.
2. Kett DH, Azoulay E, Echeverria PM, Vincent JL. Extended Prevalence of Infection in ICU Study (EPIC II) Group of Investigators. *Candida* bloodstream infections in intensive care units: analysis of the extended prevalence of infection in intensive care unit study. *Crit Care Med* 2011; 39:665–70.
3. Leroy O, Gangneux JP, Montravers P, Mira JP, Gouin F, Sollet JP et al. Epidemiology, management, and risk factors for death of invasive *Candida* infections in critical care: a multi-centre, prospective, observational study in France (2005-2006). *Crit Care Med*. 2009; 37(5):1612-8.
4. Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic shock attributed to *Candida* infection: importance of empiric therapy and source control. *Clin Infect Dis*



2012; 54:1739–46.

5. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis* 2006; 43:25–31.
6. Eggimann P, Francioli P, Bille J, et al. Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients. *Crit Care Med* 1999; 27:1066–72.
7. Pelz RK, Hendrix CW, Swoboda SM, Diener-West M, Merz WG, Hammond J et al. Double-blind placebo-controlled trial of fluconazole to prevent candidal infections in critically ill surgical patients. *Ann Surg*. 2001; 233(4):542-8.
8. Piarroux R1, Grenouillet F, Balvay P, Tran V, Blasco G, Millon L, et al. Assessment of preemptive treatment to prevent severe candidiasis in critically ill surgical patients. *Crit Care Med*. 2004; 32(12):2443-9.
9. Schuster MG, Edwards JE Jr, Sobel JD, Darouiche RO, Karchmer AW, Hadley S et al. Empirical fluconazole versus placebo for intensive care unit patients: a randomised trial. *Ann Intern Med* 2008; 149(2):83-90.
10. Ostrosky-Zeichner L, Shoham S, Vazquez J, Reboli A, Betts R, Barron MA et al. MSG-01: A randomised, double-blind, placebo-controlled trial of caspofungin prophylaxis followed by preemptive therapy for invasive candidiasis in high-risk adults in the critical care setting. *Clin Infect Dis*. 2014; 58(9):1219-26.
11. Garbino J, Lew DP, Romand JA, Hugonnet S, Auckenthaler R, Pittet D. Prevention of severe *Candida* infections in nonneutropenic, high-risk, critically ill patients: a randomised, double-blind, placebo-controlled trial in patients treated by selective digestive decontamination. *Intensive Care Med* 2002; 28:1708–17.
12. Cortegiani A, Russotto V, Maggiore A, Attanasio M, Naro AR, Raineri SM et al. anti-fungal agents for preventing fungal infections in non-neutropenic critically ill patients. *Cochrane Database Syst Rev*. 2016 Jan 16;(1):CD004920.
13. Tissot F, Lamothe F, Hauser PM, et al. β -glucan antigenemia anticipates diagnosis of blood culture-negative intraabdominal candidiasis. *Am J Respir Crit Care Med*. 2013;188(9):1100-1109.
14. Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. *Clinical Microbiology and Infection* 2012; 18 Suppl 7:19-37.
15. Leon C, Ruiz-Santana S, Saavedra P, Almirante B, Nolla-Salas J, Alvarez-Lerma F, et al. A bedside scoring system (“*Candida* score”) for early anti-fungal treatment in nonneutropenic critically ill patients with *Candida* colonization. *Crit Care Med* 2006; 34: 730–7.
16. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. *Candida* colonization and



subsequent infections in critically ill surgical patients. *Ann Surg* 1994; 220:751–758.

17. Knitsch W, Vincent JL, Utzolino S, François B, Dinya T, Dimopoulos G. A randomised, Placebo controlled Trial of Preemptive anti-fungal Therapy for the Prevention of Invasive Candidiasis Following Gastrointestinal Surgery for Intra-abdominal Infections. *Clin Infect Dis* 2015; 61(11):1671–8.
18. Posteraro B, De Pascale G, Tumbarello M, Torelli R, Pennisi MA, Bello G, et al. Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1→3)-β-D-glucan assay, Candida score, and colonization index. *Crit Care* 2011; 15:R249.
19. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, Michalopoulos A, Rafailidis PI, Falagas ME. Beta-D-glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. *Clin Infect Dis* 2011; 52:750–70.
20. Clancy CJ, Nguyen MH. Finding the “missing 50%” of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. *Clin Infect Dis* 2013; 56:1284–92



SISPCT

Bloos F, Trips E, Nierhaus A, Briegel J, Heyland DK, Jaschinski U, et al. Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock: A randomised Clinical Trial. JAMA Intern Med 2016;17(9):1266-76

Introduction

Depleted selenium levels are seen in a variety of conditions, such as systemic inflammatory response syndrome (SIRS), sepsis, trauma and in the post-operative period. Low selenium levels are associated with an increase in ICU mortality.¹ Selenium possesses antioxidant properties through selenoenzymes, it enhances glutathione peroxidase activity and improves iodine and thyroid metabolism.² However, in acute sepsis, selenium may have a transient pro-oxidant effect.² The evidence supporting selenium replacement in ICU is of poor quality, with larger, better quality trials often demonstrating no benefit.²⁻⁵

Procalcitonin, the precursor of calcitonin, is a biomarker that correlates closely with bacterial infection and outperforms other tests such as C-reactive protein and white blood cell count demonstrating better sensitivity and specificity.^{6,7} Procalcitonin levels > 1.0 ng/mL correlate with the presence of severe sepsis or septic shock and are predictive of all cause 28 day mortality.⁸ However, evidence surrounding the clinical utility of procalcitonin guided therapy in critical care is conflicting.⁸⁻⁹ In a study where procalcitonin was used to guide antimicrobial escalation, the treatment group had greater use of broad spectrum antibiotics with no mortality benefit but a greater need for mechanical ventilation and an increased length of ICU stay.⁸ In contrast, the use of procalcitonin to guide cessation of antimicrobials has been shown to reduce antibiotic usage with either a reduction or no effect on mortality.^{9,10}

Study synopsis

This multi-centre, randomised, placebo controlled trial examined the effect of sodium selenite replacement and procalcitonin-guided antimicrobial therapy in severe sepsis or septic shock. The authors hypothesised both these interventions would reduce 28 day mortality. It was assumed there was no interaction between these interventions therefore a 2 x 2 factorial design was chosen.

Patients aged ≥ 18 years were recruited from 33 ICUs in Germany between 2009 and 2013. Patients were eligible within the first 24 hours of onset of severe sepsis (defined as SIRS due to infection plus acute organ dysfunction) or septic shock (defined as sepsis plus systolic blood pressure ≤ 90 mm Hg or mean blood pressure ≤ 70 mm Hg or the need for vasopressor therapy). There were a number of exclusions, including immunocompromised patients and those with infection where guidelines recommended



prolonged courses of antimicrobials. Randomisation was conducted on a 1:1:1:1 basis and was stratified for centre, sex and sepsis severity.

Patients were randomised to receive intravenous sodium selenite (1,000 µg loading dose, followed by 1,000 µg/d) or 0.9% saline placebo until ICU discharge or 21 days. This component of the trial was blinded. In the procalcitonin component of the trial, procalcitonin was measured on days 0, 1, 4, 7, 10, and 14. Day 0 or day 1 results were taken as a baseline value. On day 4 no change in antimicrobials was recommended if the procalcitonin level had fallen by > 50%, failing this there was a recommendation to optimise or change antimicrobials or achieve source control. On days 7,10 and 14 procalcitonin levels ≤ 1 ng/mL or a drop of > 50% resulted in a recommendation to stop antimicrobials. If neither of these points were met there was a recommendation to optimise or change antimicrobials or achieve source control. Treating clinicians were allowed to overrule the recommendations. In the non-procalcitonin group antimicrobial choices were at the discretion of treating clinicians. This component of the trial was not blinded.

The primary endpoint was 28 day mortality. The study sought to detect a 10% absolute difference in 28 day mortality with a significance level of 0.05 and a 90% power. Assuming a 40% mortality in the standard treatment group (placebo with no procalcitonin guidance) and a 15% drop out rate 1,180 patients were needed in total.

8,174 patients were screened, 1,180 patients were enrolled and 1,089 patients were included in the final analysis. 87.0% of patients had septic shock. The mean APACHE II score was 24.2. There was a significant interaction between the two study groups. In the group of patients who did not receive procalcitonin guidance; those randomised to receive sodium selenite had a higher 28 day mortality (33.3%) than those randomised to placebo (22.9%) (P = 0.008). After adjustment for baseline imbalances this remained statistically significant (P = 0.03). As there was no relationship between selenium levels and procalcitonin levels the authors regarded this interaction as a chance finding and continued with the factorial analysis as planned.

There was no difference in the 28 day mortality in those treated with selenium (28.3%; 95% CI, 24.5% to 32.3%) or placebo (25.5%; 95% CI, 21.8% to 29.4%) (P = 0.30). There was no difference in 28 day mortality between the procalcitonin guided therapy group (25.6%; 95% CI, 22.0% to 29.5%) and standard care group (28.2%; 95% CI, 24.4% to 32.2%) (P = 0.34). There was no difference in 28 day mortality in the a priori subgroup analysis in either arm of the trial.

Procalcitonin guided therapy resulted in a 4.5% reduction in antibiotic exposure per 1,000 ICU days (P = 0.02). There was no difference in time to first change of antimicrobial therapy, frequency of procedures to achieve source control, costs of antimicrobial



therapy, or development of multi drug resistant pathogens. In the procalcitonin-guided therapy group the rate of protocol violation was 21.0%. By day 7, adherence to the protocol was 40.9% with clinicians justifying non-adherence due to fever, WCC changes and microbiological results. Clinicians overruled recommendations to stop antimicrobials in 50.4% of the cases. There was no difference between any of the four groups in 90 day mortality, SOFA scores, ICU or hospital length of stay, ventilator or vasopressor free days. Though selenium was associated with fewer renal replacement therapy days.

Study critique

This study comes from the SepNet group who were also responsible for the VISEP trial, another 2 x 2 factorial study in severe sepsis.¹¹ The 2 x 2 factorial design attempts to answer two seemingly unrelated questions. There was, however, a significant interaction between the two components of the trial but in demonstrating the lack of relationship between selenium levels and procalcitonin, the authors were able to alleviate concerns in this regard. The main paper and supplementary material quote in excess of 170 P values, it is unsurprising that some of these reached statistical significance. It should also be noted that due to a lower than predicted mortality, the study is slightly underpowered.

One of the most interesting aspects of this paper is the lack of impact that procalcitonin had on antimicrobial prescribing. Although procalcitonin guidance resulted in a statistically significant reduction in antibiotic exposure it may not have been clinically relevant (862 per 1000 ICU days in the control group compared with 823 in the procalcitonin guided therapy group). The authors attribute the negative trial outcome to the lack of difference in time to change of antimicrobials, total duration of antimicrobials, diagnostic procedures and source control. Clinicians failure to follow recommendations based on the procalcitonin results may be responsible for much of this. By day 7, only 40.9% of patients were following the protocol. On day 7, of the 174 cases where the protocol was not followed, 151 cases did not stop antimicrobials when recommended to do so by the procalcitonin algorithm. In the PASS trial the authors achieved an 82.1% adherence to their procalcitonin based algorithm using daily telephone calls to clinicians but crucially this was a trial pertaining to antimicrobial escalation not stopping.⁸ This raises the question was there equipoise for deescalation of antimicrobials in this trial.

The authors argue that clinicians were reluctant to change or stop antimicrobials in this group of patients (87.0% had septic shock) based on a sole biomarker. The stopping rules used may have contributed to this. Procalcitonin levels ≤ 0.5 ng/mL or a drop of $> 50\%$ resulted in a recommendation to stop antimicrobials. In the SAPS trial a fall in procalcitonin levels of $> 80\%$ from their peak value or an absolute procalcitonin level of 0.5 ng/mL resulted in a recommendation to stop antibiotics. Moreover, this was in a population where only 18.5% had septic shock. This resulted in a significant decrease in



antimicrobial use and a reduction in 28 day and one year mortality.⁹ The PRORATA trial used identical stopping criteria.¹⁰

This failure to follow the algorithm was compounded by the high protocol violation rate in the procalcitonin component of the trial. There was no difference in the rate of source control between the two groups (41.0% overall) or the rate of procedures for detection of source of sepsis (89.5%). The 28 day mortality in this trial was comparable to that seen in the PROMISE trial which examined early goal direct therapy in septic shock.¹¹ This suggests that patients as a whole were managed well, though the open nature of the study in relation to procalcitonin may have resulted in contamination between the two groups.

Ultimately this becomes a trial of selenium in septic shock (with a small number of patients included with severe sepsis). This component of the trial was well conducted. It was blinded, the patients recruited had a deficit in plasma selenium and the authors achieved good internal validity demonstrating excellent separation between plasma selenium levels of the two groups from the time of the first bolus until day 14. Previous studies have been criticised for inadequate dosing of selenium, inadequate duration of infusion and recruiting patients who had normal plasma selenium levels.² This paper addresses these issues. There was two potential confounding variables that may have diluted the treatment effect of selenium; the use of sodium selenium was 11.4% prior to trial enrolment and the use of other anti-oxidants was high (41.5% of patients received N-acetylcysteine). However, these confounding variables were evenly distributed across all four groups and therefore should not have impacted on trial outcomes.

In light of the limitations highlighted above, very few conclusions can be drawn in relation to the use of procalcitonin in severe sepsis or septic shock. There is a growing body of evidence that demonstrates that lack of benefit from selenium.

Where this sits in the body of evidence

The PASS trial randomised 1,200 ICU patients to receive standard care or daily procalcitonin levels with an associated antimicrobial escalation algorithm. Antimicrobials were up escalated if a procalcitonin was > 1.0 ng/mL or had not decreased by $> 10\%$ from the previous day. There was no difference in the primary endpoint of 28 day mortality; 31.5% in the procalcitonin arm versus 32.0% in the standard care arm. Patients in the procalcitonin group had an increased ICU length of stay ($P=0.004$) and higher rate of mechanical ventilation. The protocol resulted in an increase in the use of Piperacillin/tazobactam ($P<0.001$) and Cefuroxime ($P<0.001$) with no effect on the use of Meropenem ($P=0.23$) and a reduction in the use of Ciprofloxacin ($P<0.001$).⁸

The SAPS trial was a prospective, multi-centre, randomised, controlled, trial involving 1,546 critically ill patients who had received their first dose of antibiotics in the last 24



hours. This study compared procalcitonin guided discontinuation of antimicrobials with standard care. Clinicians were advised to stop antimicrobials if procalcitonin decreased by 80% of its peak or an absolute value of ≤ 0.5 ng/mL. Only 18.5% of this study population had septic shock. Procalcitonin guided therapy resulted in a reduction in the antibiotic daily defined doses (absolute difference, 2.69; 95% CI, 1.26 to 4.12; $P < 0.0001$) and duration of antimicrobial treatment; 5 days vs 7 days (absolute difference, 1.22; 95% CI 0.65 to 1.78; $P < 0.0001$). There was also a reduction in the secondary endpoint of 28 day mortality (20.5% vs 25%; $P = 0.0122$), this persisted up to one year ($P = 0.0188$). There was no difference in the need for repeated course of antibiotics ($P = 0.67$).⁹

The PRORATA study was multi-centre, randomised, open-label trial of 621 ICU patients. In this trial, procalcitonin levels were used to guide starting and stopping of antibiotics in comparison to standard care. The primary end points were 28 and 60 day mortality (non-inferiority) and days without antibiotics (superiority). There was no difference in mortality between the two groups at 28 days (procalcitonin group, 21.2% vs standard care group, 20.4%; absolute difference, 0.8%; 90% CI, - 4.6 to 6.2) and 60 days (30.0% vs 26.1%; absolute difference, 3.8%, 90% CI - 2.1 to 9.7). Procalcitonin guided therapy resulted in significantly more days without antibiotics in the first 28 days (14.3 days vs 11.6 days; absolute difference, 2.7 days; 95% CI, 1.4 to 4.1; $P < 0.0001$).¹⁰

In an observational study plasma selenium levels were measured in 134 consecutive ICU patients. The mean plasma selenium level was low 0.68 ± 0.23 $\mu\text{mol/L}$. There was a weak negative correlation between plasma selenium and APACHE II ($r^2 = 0.11$, $P < 0.0001$) and SAPS II ($r^2 = 0.09$, $P < 0.001$). Patients with a plasma selenium level of ≤ 0.7 $\mu\text{mol/L}$ had a mortality of 25% compared to 7% in those with a plasma selenium level of > 0.7 ($P < 0.01$). This group also were 3.5 times more likely to develop a complication whilst in ICU.¹

A meta-analysis was conducted looking at selenium (at doses ≥ 100 $\mu\text{g/day}$) compared to placebo in patients with SIRS, sepsis and septic shock. A total of 792 patients from 9 trials were included. Only two papers were at low risk of bias, overall the quality of evidence was assessed to be low. Selenium was associated with a reduced mortality (OR, 0.73; 95% CI, 0.54 to 0.98; $P = 0.03$). There was no impact on ICU length of stay (mean difference, 2.03; 95% CI, -0.51 to 4.56; $P = 0.12$). The two papers with low risk of bias demonstrated no difference in mortality.²⁻⁴

502 adult ICU / HDU patients requiring parenteral nutrition were randomised to receive parenteral glutamine (20.2 g/day), selenium (500 $\mu\text{g/day}$), or both. The primary endpoints were new infection and mortality. Selenium did not increase the rate of new infection (OR, 0.81; 95% CI, 0.57 to 1.15), except in those who had ≥ 5 days of selenium (OR, 0.53; 95% CI, 0.30 to 0.93). There was no effect on six month mortality (OR, 0.89; 95% CI, 0.62 to 1.29).³



60 patients with SIRS or sepsis were randomised to receive high dose selenium (4,000 µg on day 1, followed by 9 days of 1,000 µg/day) or placebo. There was no difference in time to vasopressor withdrawal ($P = 0.713$), duration of mechanical ventilation ($P = 0.762$) or mortality at 7, 14, 28 and 180 days and 1 year after randomisation.⁴

In a 2 x 2 factorial trial, 1,223 patients requiring mechanical ventilation and with at least two organ failures were randomised to receive placebo, glutamine, antioxidants or both. Antioxidants included selenium, zinc, beta carotene, vitamin E and vitamin C. Due to the interim-analysis plan, a P value of less than 0.044 was set. Glutamine supplementation was associated with an increased 28 mortality, though this did not reach statistical significance (32.4% vs 27.2%; adjusted OR, 1.28; 95% CI, 1.00 to 1.64; $P = 0.05$). In hospital mortality ($P=0.02$) and 60 day mortality ($P=0.02$) were both significantly higher in those treated with glutamine. There was no difference in 28 day mortality between those who received antioxidants (30.8%) and those who received placebo (28.8%) (adjusted OR, 1.09; 95% CI, 0.86 to 1.40; $P=0.48$).⁵

Should we implement this into our practice?

There is currently no strong evidence to support the use of selenium. The role of procalcitonin in relation to antimicrobial commencement and cessation requires further research.

References

1. Forceville X, Vitoux D, Gauzit R, Combes A, Lahilaire P, Chappuis P. Selenium, systemic immune response syndrome, sepsis, and outcome in critically ill patients. *Crit Care Med*. 1998 Sep;26(9):1536–44.
2. Alhazzani W, Jacobi J, Sindi A, Hartog C, Reinhart K, Kokkoris S, et al. The effect of selenium therapy on mortality in patients with sepsis syndrome: a systematic review and meta-analysis of randomised controlled trials. *Crit Care Med*. 2013 Jun;41(6):1555–64.
3. Andrews PJD, Avenell A, Noble DW, Campbell MK, Croal BL, Simpson WG, et al. Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. *BMJ*. 2011 Mar 17;342:d1542.
4. Forceville X, Laviolle B, Annane D, Vitoux D, Bleichner G, Korach J-M, et al. Effects of high doses of selenium, as sodium selenite, in septic shock: a placebo-



- controlled, randomised, double-blind, phase II study. *Crit Care*. 2007;11(4):R73.
5. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomised Trial of Glutamine and Antioxidants in Critically Ill Patients. *N Engl J Med*. 2013;368(16):1489–97.
 6. Luzzani A, Polati E, Dorizzi R, Rungatscher A, Pavan R, Merlini A. Comparison of procalcitonin and C-reactive protein as markers of sepsis. *Crit Care Med*. 2003 Jun;31(6):1737–41.
 7. Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da Dalt L. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. *Pediatr Infect Dis J*. 2007 Aug;26(8):672–7.
 8. Jensen JU, Hein L, Lundgren B, Bestle MH, Mohr TT, Andersen MH, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomised trial. *Crit Care Med*. 2011 Sep;39(9):2048–58.
 9. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *The Lancet Infectious Diseases*. 2016 Jul;16(7):819–27.
 10. Bouadma L, Luyt C-E, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multi-centre randomised controlled trial. *The Lancet*. 2010 Feb;375(9713):463–74.
 11. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al. Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis. *N Engl J Med*. 2008;358(2):125–39.
 12. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al for the ProMISe Trial Investigators. Trial of Early, Goal-Directed Resuscitation for Septic Shock. *N Engl J Med*. 2015 ;372(14):1301–11.



Protein C Zymogen

Pappalardo F, Crivellari M, Di Prima A, Agracheva N, Celinska-Spodar M et al
Protein C zymogen in severe sepsis: a double-blinded, placebo-controlled, randomised study. *Intensive Care Med* 2016; 42(11):1706–1714

Introduction

Significant efforts have been made to elucidate the complex interactions of the cellular and humoral components of the inflammatory, coagulation and immunomodulatory cascades that characterise the host response to severe sepsis. To date, pharmacotherapies based on candidate molecules derived from this have been disappointing.^{1,2} The most established in clinical practice was Activated Protein C (APC, drotrecogin alfa (activated), marketed by Eli Lilly as Xigris®); an endogenous anti-thrombotic compound with anti-inflammatory and fibrinolytic properties with the potential to ameliorate the microvascular thrombosis seen in sepsis-related disseminated intravascular coagulation (DIC). An initial survival benefit seen with its use in septic patients led to widespread use and advocacy, albeit with concern about bleeding risk and doubt about the significance of benefit. A more recent multi-centre trial was unable to replicate the prior positive result and the drug was withdrawn worldwide.³

It is possible the well-documented bleeding risk with APC is sufficient to negate an otherwise clinically useful effect. The native Protein C zymogen (PCZ) is inert until activated by endothelial receptors and thrombin-thrombomodulin complexes; the consumption of which gives a biologically plausible self-limitation of the amount of APC in circulation and hence bleeding risk.⁴ Haematologists use PCZ as replacement therapy in congenital or acquired deficiency syndromes, treating venous thrombosis or purpura fulminans, where it seems both safe and effective. It has been used off-license in both paediatric and adult patients with severe sepsis (and presumed consumptive PCZ deficiency) with data limited to case reports or series.⁵

Study synopsis

This study is the first to test PCZ in a randomised controlled trial (RCT) in adults with severe sepsis or septic shock. Adult patients were screened at a single Italian ICU over a 2-year period; institutional ethical approval and individual patient or surrogate consent were secured. To be eligible patients required a sepsis diagnosis alongside an additional component suggesting a high mortality risk - Extracorporeal membrane oxygenation (ECMO); disseminated intravascular coagulopathy (DIC); >2 organ failures or APACHE II score >25. Randomisation was by computer-generated block and delivered in sealed envelopes. PCZ or matching volume saline placebo was infused over 72 hours (50 IU/kg bolus followed by 3 IU/kg/hr).



The chosen primary endpoint was a composite of mortality or ongoing ICU stay at 30 days. Multiple secondary outcomes included length of stay variables, bleeding or thrombotic complications and effects on laboratory data. The desired 80% power at 0.05 significance level to detect the anticipated 33% absolute decrease in the treatment group primary endpoint rate (50% vs 75%) required the enrolment of 116 patients. No interim analysis was planned. All analyses were by intention-to-treat, the χ^2 (or Fisher's exact) test was used for categorical data including the primary endpoint. The Italian Ministry of Health funded the study.

The study was stopped early by the Italian Medicines agency due to a high overall mortality rate; at this stage 54 eligible patients had been identified over a 2-year period. 16 were excluded (5 declined, 11 were entered into a different study). 38 patients were randomised, 18 to placebo and 20 to PCZ, of whom 1 patient later withdrew consent. Mean age was 65, 73% were male and 97% white. Twenty post-operative (13 of which cardiac surgery) were included. Patients were randomised after a median of 3.5 / 2 days (placebo / PCZ) in ICU, but within a median of 1.5 hours of meeting inclusion criteria in both groups.

Severity of illness was high: mean APACHE II score was 25 / 25 and mean SAPS II score 63 / 60 in the placebo / PCZ groups. 32 (86%) were ventilated; 35 (95%) received vasoactive agents; 12 (32%) patients had an intra-aortic balloon pump (IABP) and veno-venous ECMO was used in 3 placebo and 7 PCZ patients (27% overall). Antiplatelet and anticoagulant use was common, with unfractionated heparin (8 placebo, 5 PCZ) the commonest and a total of 15 other drug uses recorded across all patients. Patients were coagulopathic at baseline, 8 meeting DIC criteria and a mean platelet count of $97 \times 10^9/l$ and mean INR of 1.9 in the PCZ group. There were no significant between-group differences in any baseline characteristic except for a higher C-reactive protein in the placebo group (mean 319 vs 195 in PCZ group). Protein C Zymogen infusion was interrupted in 7 patients (4 died, 2 left ICU, 1 error) and given for a mean \pm SD of 61 ± 17 hours (placebo 61 ± 17 hours). There were no documented adverse reactions.

There was no difference in the primary endpoint (prolonged ICU / death rate was 79% in the PCZ group and 67% in placebo, $p=0.4$). ICU and hospital mortality was significantly higher with PCZ but not significantly different at 30 or 90 days (ICU PCZ /placebo mortality 79% vs 39%, $P=0.020$; day 90 mortality 79% vs 50%, $P=0.091$). Kaplan-Meier analysis confirmed a significantly increased survival time in the placebo group ($P=0.035$) and PCZ infusion was a significant predictor of ICU mortality on multivariate logistic regression analysis (OR, 5.0; 95% CI, 1.45 to 17.3; $P=0.011$). There were no significant differences in any of the 17 other secondary outcomes or laboratory coagulation tests, 12 patients were transfused in each group.



Study critique

This study has strengths, aiming to use a RCT to establish an evidence base for an expensive drug that was increasingly being used off-license in sepsis. There was biological plausibility and supportive paediatric and adult case series.⁶ Randomisation was concealed, study drug administration was effectively blinded and follow up was complete with 90-day mortality data available for all patients. However, commentary pieces published since the worldwide withdrawal of APC have suggested that future sepsis research should aim to redress past failings in the area, many of which are pertinent to this paper.^{1,2}

Patient selection in sepsis trials is difficult due to the diverse clinical and pathophysiological entities that comprise the syndrome. Systemic inflammatory response syndrome (SIRS) criteria and common laboratory tests (WCC, CRP) are non-specific especially in a population with established critical illness. Investigation of >100 biomarkers has failed to identify those with the necessary sensitivity, specificity and predictive value to specify a homogenous trial population.⁷ Microbiological culture results are frequently delayed or negative in patients with a clinical diagnosis of severe sepsis.¹

In future trials the use of direct bacterial genetic probes and the newer Sepsis-3 definitions may help. A large study population rigorously meeting the internationally agreed sepsis criteria where differences may even out may best serve trials of generic supportive therapies. In a small trial testing a specific endogenous mediator such as PCZ it may have been preferable to target a discrete clinical population such as those with septicaemia and purpura fulminans where the pathophysiology may be more convergent. This was the setting of much of the previous paediatric use of PCZ.⁶

Unfortunately the population in this study was extremely heterogeneous with many admitted to ICU for non-septic reasons such as cardiac failure. There was a median of 3 days before the chosen sepsis criteria were met and the patient could be randomised, suggesting if infection was present at all it was likely to be predominantly hospital-acquired secondary infection at an early stage; and the identified high risk of death may not have been ameliorable to a sepsis-targeted intervention. The microbiological data supplied shows that 28 (76%) had a positive culture, but these were diverse in site and organism, for example, 16 (43%) had fungi isolated, which may reflect colonisation as opposed to infection.

Over half of the patients were receiving mechanical cardiorespiratory support with 12 (32%) having an IABP in situ at enrolment, and 10 (27%) receiving veno-venous ECMO. As well as suggesting possible refractory cardiac or respiratory failure these therapies often require full systemic anticoagulation (unless the patient is already severely coagulopathic), which may conceivably interact with the anticoagulant action of PCZ and



increase bleeding risk. This also limits the applicability of the study to populations not requiring these therapies.

Study recruitment was halted early despite the chosen primary endpoint not being significantly disadvantageous in the intervention group and there being no planned interim analysis time point. The given reason was a high overall mortality but this was not markedly different to that predicted by the SAPS II (score 61, expected mortality 71%, observed 30 day mortality 54%). There was a statistically significant difference in ICU mortality but the low patient numbers mean this was a fragile result and if 2 fewer patients had died in the PCZ arm significance would have been lost (it is notable in this context that one PCZ patient withdrew consent and was excluded from the analysis).⁸ Also of note mortality was significantly increased at geographically determined time points (in-ICU and in-hospital) but not at 30 or 90 days.

The use of a composite primary endpoint is questionable, especially the combination of two metrics (30-day mortality with 30-day ICU stay) which are not of equal clinical importance. In this study mortality comprised 58% of the primary outcome events in the control group and 87% in the PCZ group. Composite outcomes are inherently susceptible to bias, either by having components that are partly clinician determined (such as ICU discharge date) or by potentially including variables post hoc to achieve statistical significance.⁹ If the intervention was hoped to impact on ICU length of stay then a better primary outcome in this small trial may have been ICU-free days or ventilator-free days, with mortality as a secondary endpoint.

In this study there were no identified adverse reactions, bleeding or thrombosis events with PCZ, which might have suggested a mechanism of harm and that the observed mortality risk was more likely to be causal. Supplementary data supplied showed that PCZ seemed to have little effect on any laboratory marker of coagulation, which was in contrast to that seen in non-randomised studies (some of which used a higher dose).⁵ Simulation of possible trial outcomes if recruitment continued suggested a significantly beneficial effect of PCZ was highly unlikely, but completed “negative” trials can reveal important data on safety and suggest areas for future study. The anticipated 33% relative (25% absolute) reduction in the primary endpoint was optimistic and a negative study would not have excluded a smaller clinically relevant benefit. Finally measuring PCZ levels at baseline, during and following infusion could have aided understanding of these results and informed future studies.

In summary this trial showed no benefit of PCZ in a small heterogeneous group of critically ill patients at a high risk of death, but does not advance knowledge of its use beyond this.



Where this sits in the body of evidence

There are no other significant published RCTs investigating PCZ. The relevant literature includes those studying APC (all sponsored by Eli-Lilly) and case series.

In 2001 the PROWESS study group published the results of randomising 1690 patients with severe sepsis (SIRS criteria and organ failure) to 96 hours of 24 µg/kg/hr of APC or placebo.¹⁰ The trial was stopped early for efficacy. 28-day mortality was reduced in the APC group (24.7% vs 30.8%; ARR, 6.1%, 95% CI, 1.9 to 10.4%; P=0.005). Bleeding was non-significantly higher in the APC group (3.5% vs 2.0%; P=0.06).

In 2005 the ADDRESS study group randomised 2650 patients with less severe sepsis (SIRS criteria and APACHE II <25 or single organ failure) to 96 hours of 24 µg/kg/hr of APC or placebo.¹¹ The study was stopped early for futility, with no difference in the primary outcome of 28-day mortality (APC, 18.5% vs placebo 17.0%; RR, 1.08; 95% CI, 0.92 to 1.28; P=0.34). Serious bleeding events were more common with APC by day 28 (3.9% vs 2.2%, P=0.01).

In 2007 the RESOLVE study group published the results of randomising 477 children with severe sepsis (SIRS with cardiovascular and respiratory failure) to 96 hours of 24 µg/kg/hr of APC or placebo.¹² Median age was 2.5 years, 32% were <1 year old. The study was stopped early for futility. There was no difference in the primary endpoint (time to organ failure resolution) or mortality (28-day mortality 17.2% (APC) vs 17.2% (placebo), P=0.93). The numerical increase in CNS bleeding events with APC at day 28 (11 vs 5) was not statistically significant.

In a 2012 European Medicines Agency mandated follow-up study the PROWESS-SHOCK study group randomised 1697 patients with septic shock (SIRS, vasopressors and hypoperfusion) to 96 hours of 24 µg/kg/hr of APC or placebo.¹³ There was no difference in the primary outcome of 28-day mortality (26.4% with APC vs 24.2% with placebo; RR, 1.09; 95% CI, 0.92 to 1.28; P=0.31). Non-serious bleeding events were significantly increased in the APC group (8.6% vs 4.8%; RR 1.8; 95% CI, 1.23 to 2.61; P=0.002) but serious or CNS bleeding was not different. Eli-Lilly withdrew APC from worldwide markets following this publication.

In a 2003 Dutch phase 2 dose-finding study de Kleijn et al randomised 40 children with meningococcal septic shock and purpura fulminans to placebo or 3 different doses of PCZ (200, 400 or 600IU/kg 6-hourly for 3 days then 12-hourly for 4 days).¹⁴ Median age was 2.3 years. Plasma PCZ and APC levels increased with active drug in a dose-dependent manner; there was a corresponding fall in plasma d-dimer levels. There was one minor bleeding event. 5 of the 7 deaths in the APC arms were in the 150 IU/Kg group with a lower mortality than predicted by Rotterdam score in the 50 and 100 IU/kg arms. A phase 3 trial was suggested.



In a poster presentation published as an abstract Morelli et al randomly assigned 36 septic patients to 72 hours of PCZ (3 IU/kg/hr) or standard treatment.¹⁵ There was no effect seen of PCZ on microcirculatory flow.

In 2007 Barrato et al described 20 patient with severe sepsis and clinical contraindications to APC who were given PCZ (3 IU/kg/hr for 72 hours, adjusted to maintain plasma PC activity at 70-120% normal levels) in a pilot study.⁴ Baseline PCZ activity was $34.5 \pm 9.1\%$, PCZ infusion normalised levels within 48 hours. SOFA scores, lactate levels and DIC score fell during the study period, 28-day mortality was 35%. There were no noted bleeding complications despite risk factors such as thrombocytopenia, major surgery and anticoagulant drugs, the investigator suggested evaluation of PCZ in those unable to receive APC.

In 2012 Crivellari et al published a prospective case series of 23 adult patients with severe sepsis and contraindications to APC who were given PCZ infusions (50 IU/kg bolus then 3 IU/kg/hr for 72 hours).¹⁶ 18 (78%) were post cardiac surgery. Plasma PCZ levels were normalised by the infusion, no bleeding events were reported. Observed mortality (30%) was less than the given expected 53%, although the chosen method for predicting mortality was not stated and it was acknowledged that post-operative / post cardiac bypass SIRS may have confounded the diagnosis of sepsis in the population. The same authors had published a case series comprising 9 of the post-cardiac surgical patients included in this study in 2009.¹⁷

In 2013 Landoni et al in a systematic review assessed 1,577 potential titles and selected 28 which related to the use of PCZ in 340 septic patients (232 children, 108 adults) without congenital deficiency.⁵ 26 studies were case series with the largest comprising 94 paediatric patients with purpura fulminans and 12 studies comprising less than 5 patients. The 2 RCTs included are described above. Overall mortality was 20.6%. Most studies reported improved markers of inflammation and/or coagulation and mortality less than expected for the severity of disease. Bleeding complications were described in 3 patients.

Should we use Protein C zymogen in sepsis?

No. This therapy should not be used outside of the setting of a clinical trial.

References:

1. Opal SM, Dellinger RP, Vincent J-L, Masur H, Angus DC. The Next Generation of Sepsis Clinical Trial Designs: What Is Next After the Demise of Recombinant Human Activated Protein C? *Crit Care Med* 2014;42(7):1714–21.
2. Cohen J, Opal S, Calandra T. Sepsis studies need new direction. *Lancet Infect Dis* 2012;12(7):503–5.
3. Vincent J-L. The rise and fall of drotrecogin alfa (activated). *Lancet Infect Dis* 2012;12(9):649–51.
4. Baratto F, Michielan F, Meroni M, Dal Palù A, Boscolo A, Ori C. Protein C concentrate to restore physiological values in adult septic patients. *Intensive Care Med* 2008;34(9):1707–12.
5. Landoni G, Silveti Si, Crivellari M, Mucchetti M, Taddeo D. Administration of protein C concentrates in patients without congenital deficit: a systematic review of the literature. *Signa Vitae* 2013;8(2):15–9.
6. Veldman A, Fischer D, Wong FY, et al. Human protein C concentrate in the treatment of purpura fulminans: a retrospective analysis of safety and outcome in 94 pediatric patients. *Crit Care* 2010;14(4):R156.
7. Pierrakos C, Vincent J-L. Sepsis biomarkers: a review. *Crit Care* 2010;14(1):R15.
8. Ridgeon EE, Young PJ, Bellomo R, Mucchetti M, Lembo R, Landoni G. The Fragility Index in multi-centre randomised Controlled Critical Care Trials*: *Crit Care Med* 2016;44(7):1278–84.
9. Cordoba G, Schwartz L, Woloshin S, Bae H, Gotzsche PC. Definition, reporting, and interpretation of composite outcomes in clinical trials: systematic review. *BMJ* 2010;341(aug18 3):c3920–c3920.
10. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344(10):699–709.
11. Abraham E, Laterre P-F, Garg R, et al. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005;353(13):1332–41.
12. Nadel S, Goldstein B, Williams MD, et al. Drotrecogin alfa (activated) in children with severe sepsis: a multi-centre phase III randomised controlled trial. *Lancet Lond Engl* 2007;369(9564):836–43.
13. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin Alfa (Activated) in Adults with Septic Shock. *N Engl J Med* 2012;366(22):2055–64.
14. de Kleijn ED, de Groot R, Hack CE, et al. Activation of protein C following infusion of protein C concentrate in children with severe meningococcal sepsis and purpura fulminans: A randomised, double-blinded, placebo-controlled, dose-finding study: *Crit Care Med* 2003;31(6):1839–47.



15. Morelli A, Donati A, Di Russo A, et al. Human protein C concentrate to restore physiological values in adult septic shock patients: effects on microcirculation. *Crit Care* 2012;16(Suppl 1):P201.
16. Crivellari M, Silveti S, Gerli C, et al. Protein C zymogen in adults with severe sepsis or septic shock. *Med Intensiva* 2014;38(5):278–82.
17. Crivellari M, Della Valle P, Landoni G, et al. Human protein C zymogen concentrate in patients with severe sepsis and multiple organ failure after adult cardiac surgery. *Intensive Care Med* 2009;35(11):1959–63.



SMOOTH

Schmidt K, Worrack S, Von Korff M, Davydow D, Brunkhorst F, Ehlert U et al. Effect of a Primary Care Management Intervention on Mental Health-Related Quality of Life Among Survivors of Sepsis – A Randomised Clinical Trial. JAMA 2016;315(24):2703-2711

Introduction

Surviving sepsis is associated with a greater than 3-fold increase in the prevalence of cognitive impairment and functional limitation which persists for years after the precipitating episode.¹ The public health implications and healthcare costs of sepsis, and its sequelae, are enormous – in 2011 over \$20 billion was spent in the US alone.²

The reduction in health-related quality of life and increased burden on family members and caregivers is becoming ever more apparent.³ In the years 1999 to 2008 3-year survivorship from sepsis, in those aged over 65, increased by an estimated 119%. 17% of survivors were estimated to be suffering moderate-to-severe cognitive impairment and 75% were estimated to require help with at least 1 activity of daily living.⁴ Many of the issues from which survivors of sepsis struggle will only become apparent to the primary care physician (PCP) who looks after the patient in the community setting. Specific interventions for this patient group have not been developed within the primary care setting. Furthermore, educational support for the primary care physician and the community healthcare team is an area which has been to date unexplored.

Study synopsis

The primary hypothesis in this trial was that a primary-care based intervention would improve mental-health related quality of life among survivors of sepsis compared with usual care.

The intervention consisted of three core components;

- Case management focusing on proactive patient symptom monitoring
- Clinical decision support for the PCP
- Training for both patients and PCPs in evidence-based care

Adult patients who had suffered severe sepsis or septic shock were recruited from 20 ICUs in 9 study centres across Germany. Clinical diagnosis of sepsis was made by the treating intensivists according to internationally recognised definitions. Baseline interviews were carried out with patients within 1 month of ICU discharge. Patients with severe cognitive impairment, as determined by the Telephone Interview of Cognitive Status (score ≤ 27), were excluded. Once eligibility of the patient was confirmed, the study invited each patient's PCP to participate. Randomisation was stratified by ICU



centre and performed by computer-generated random permuted blocks (size range 2 to 6).

Three experienced ICU nurses were trained as outpatient case managers during an 8 hour workshop. Case managers met with patients for the first time a median of 8 days post-ICU discharge (IQR 2 to 20). The first meeting focused on educating the patient on sepsis sequelae using a Sepsis Help Book. Patients were then telephone interviewed monthly for 6 months then once every 3 months for the last 6 months of the trial. Validated screening tools were used to monitor patients symptoms as well as patient self-management behaviours such as physical activity and individual self-management goals.

A consulting physician, with a background in primary and ICU care, supervised and received reports from each case manager. Consulting physicians also provided clinical decision support to PCPs using a structured written report using a traffic light system – red “requires immediate intervention,” amber “consider intervention” and green “acceptable clinical status.” Evidence-based sepsis aftercare training was provided for the PCP, on an individual basis, by the consulting physician utilizing a Sepsis PCP manual. The intervention was deemed to have high integrity if both patients and PCPs received training and the patient was monitored ≥ 5 times. The control group received usual care from PCPs without any additional information or monitoring.

The primary outcome was change in mental health-related quality of life between ICU discharge and 6 months after ICU discharge as assessed by the Mental Component Summary (MCS) score of the 36-item Short Form Health Survey (SF-36 [range 0-100; higher scores indicate lower levels of impairment]). A total of 31 secondary outcomes relating to patient health and process of care were identified and derived at 6 and 12 months post-ICU discharge. Data was analysed according to the Intention-To-Treat (ITT) principle.

An initial sample size of 287 was required to detect a difference of 5 points or more in the mean MCS score at 6 months (power 90%, $\alpha = 0.05$). Of 682 patients screened, 361 patients met inclusion criteria. 80.6% (n=291) of patients were recruited - 148 patients to the intervention group and 143 patients to the control group. Both groups were well matched at baseline with a mean (SD) MCS score close to that of the background German population 49 (12.5).

95.8% (n=294) PCPs were willing to participate in the trial. 22.7% (n=66) of patients were lost to follow-up at 6 months with an additional 6.2% at 12 months. 70.3% (n=104) of patients were deemed to have received high integrity intervention (experiencing all 3 intervention components). 87.8% (n=130) of patients received training from case managers and 84.5% (n=125) of PCPs received training from a consulting physician. Most



cases of incomplete intervention were due to death of the patient.

The mean change in MCS score did not differ significantly between groups - 3.79 (95% CI, 1.05 to 6.54) vs 1.64 (95% CI, 1.22 to 4.51) in intervention vs control groups, respectively (P=0.28). 63 secondary outcomes were analysed at 6 and 12 months. At 6 months, hypothesis generating secondary outcome effects were seen in the intervention group only in functional outcomes, with the intervention group having better physical functioning, less physical disability and fewer ADL impairments than those receiving usual care. At 12 months those in the intervention group had potentially fewer sleep impairments.

Study critique

This is the first large scale randomised, controlled trial of an intervention aimed at improving outcomes of sepsis survivors in the primary care setting. Schmidt and colleagues have demonstrated it is possible to set up and complete a trial, with a high degree of integrity and relatively low dropout rate in this setting. Why was no effect on MCS demonstrated? The baseline mental health-related quality of life of this cohort was similar to that of the general German population thus the capacity for the intervention to improve the MCS score may have been limited. Patients with more severe cognitive dysfunction were excluded in this study but perhaps the patients with cognitive dysfunction post-ICU are the very people who should be targeted by post-ICU interventions. By targeting a group of patients with more severe cognitive or psychological sequelae as a result of the ICU admission a difference in mental health-related quality of life may become more demonstrable. The heterogeneity of the patient population and the variety of physical, psychological and social problems post-sepsis patients suffer may have impacted on the ability of this intervention to provide meaningful quantitative outcomes. Future studies may need to focus on a more specific intervention on specific patient subgroups and/or sepsis sequelae.

Process data from the control group indicates that usual post-sepsis primary care in Germany has a high intensity. Perhaps the intervention failed to improve on an already highly organized and proactive primary care approach. The control group were also subject to telephone calls from the case managers in order to collect follow-up data. This may have modified behaviour in the control group (Hawthorne effect) thereby leading to an underestimation of the intervention effects. Was the correct primary outcome measure chosen? One of the challenges facing investigators is actually selecting the correct primary outcome measure as more than 250 instruments to measure health-related quality of life, physical function, cognition and mental health outcomes are available.⁵ This clearly demonstrates the complexity of the post-ICU experience and the uncertainty over how to record quantitatively that experience.

NICE guidelines recommend regular assessment and individualized rehabilitation

programs from the time of ICU admission until 2 to 3 months post-ICU discharge. Less than 30% of UK Trusts provide a formal post-ICU rehabilitation service.⁶ In the PRaCTICAL study discussed below a third of patients required onward medical specialist referral with a further third requiring onward psychological referral. ICU doctors were involved in the care of approximately 50% of patients at the follow-up clinics. The need for multidisciplinary input post-ICU appears to be present but quantitative evidence for the efficacy of interventions aimed at improving physical, cognitive and emotional wellbeing remains lacking at present. Perhaps more qualitative outcomes are required. How to design and deliver effective multidisciplinary interventions for these complex patients will continue to be the subject of intense research in the coming years.

Where this sits in the body of evidence

The PRaCTICaL study was a pragmatic, non-blinded, multi-centre randomised controlled trial in which the clinical and cost effectiveness of nurse led follow-up clinics was studied.⁷ The intervention consisted of a manual based self-directed physical rehabilitation programme during which patients monitored their own compliance and progress. Nurse led clinics were held at 3 months and 9 months after ICU discharge. More than 90% of participants had the main elements of the intervention delivered. Of the 286 patients recruited 192 completed follow-up at 1 year. Health related quality of life did not differ between groups at 12 months. Follow-up clinics were significantly more expensive than standard care – mean cost £7,126 vs £4,810 for intervention vs control respectively.

In order to assess the role of early physical and occupational therapy on functional recovery 104 mechanically ventilated patients were randomised to early exercise and mobilization during daily sedation breaks or to sedation break and standard care as directed by the treating physician.⁸ The primary endpoint was the number of patients returning to independent functional status at hospital discharge. Return to independent functional status was significantly greater in the treatment group vs control group; 59% vs 35%; OR, 2.7; 95% CI 1.2 to 6.1; P=0.02.

Walsh et al completed a parallel-group randomised clinical trial of 240 patients discharged from ICU in 2 Scottish hospitals.⁹ Both intervention and control groups received physiotherapy and occupational therapy alongside speech and language therapy. The intervention group had a dedicated rehabilitation practitioner which lead to a 2 to 3 fold increase in the frequency of the exercise and mobility therapies, used individualized goal-setting and provided greater illness-specific information. The primary outcome measure was the Rivermead Mobility Index (RMI) at 3 months (range 0-15 with higher scores indicating greater mobility). At 3 months no significant difference in RMI between groups was detected (mean difference -0.2; 95% CI, -1.3 to 0.9; P=.71).

In an effort to assess the impact of a physical rehabilitation programme on the

functional recovery of ICU patients, patients were randomised to a home-based, graded individualized endurance and strength training programme supported by an illustrated exercise manual.¹⁰ The intervention (n=97) group undertook an 8 week programme focusing on strength training and walking, with 3 physical trainer home visits at weeks 1, 3 and 6. The control group (n=98) received usual community based care. Participants in both groups were assessed in-home at weeks 1, 8 and 26. Both groups showed similar improvements in SF-36 physical function score (primary outcome) and 6-minute walk test at 8 weeks which persisted at 26 weeks.

In a single-centre, assessor-blinded randomised controlled trial patients were randomised to usual care or to intensive exercises in ICU, on the ward and in the outpatient setting for 8 weeks should they be discharged from hospital.¹¹ 150 participants were assessed at ICU admission, recruitment, hospital discharge and at 3, 6 and 12 months. The primary outcome measure was the 6 minute walk (6MWT) test at 12 months. Although the intervention group had significantly lower 6MWT scores at ICU discharge, there was no significant difference in 6MWT at any other time point during follow-up, including at 12 months.

In order to evaluate the effectiveness of a rehabilitation program following critical illness to aid physical and psychological recovery, Jones et al carried out a randomised controlled trial at 3 hospitals.¹² Control patients were followed up on the ward, had three telephone calls at home and were invited to attend clinic at 8 weeks and 6 months post-discharge. The intervention group had the above but in addition they received a 6 week self-help rehabilitation manual. The intervention group had significantly better results on the SF-36 physical function scores at 8 weeks and 6 months (P=0.006). There was also a trend towards lower rate of depression at 6 months in the intervention group (12% vs 25%).

A Cochrane Review published in 2015¹³ concluded that the small number of randomised controlled trials, the heterogeneity of the interventions and primary outcome measures used mean that the effects of exercise programmes on rehabilitation following ICU admission are still unknown.

Should we implement this into our practice?

No. This study does not support the implementation of a primary care management intervention to improve mental health-related quality of life among sepsis survivors.

References

1. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *Jama* 2010;304(16):1787–94.
2. Torio CM, Andrews RM. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2011: Statistical Brief #160 [Internet]. In: Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006 [cited 2016 Dec 22]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK169005/>
3. Winters BD, Eberlein M, Leung J, Needham DM, Pronovost PJ, Sevransky JE. Long-term mortality and quality of life in sepsis: a systematic review. *Crit Care Med* 2010;38(5):1276–83.
4. Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population Burden of Long-Term Survivorship After Severe Sepsis in Older Americans. *J Am Geriatr Soc* 2012;60(6):1070–7.
5. Goddard SL, Adhikari NK. The Challenging Task of Improving the Recovery of ICU Survivors. *JAMA* 2016;315(24):2671–2.
6. Tan T, Brett SJ, Stokes T. Guidelines: Rehabilitation after critical illness: Summary of NICE guidance. *BMJ* 2009;338(7697):767–9.
7. Cuthbertson BH, Rattray J, Campbell MK, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. *BMJ* [Internet] 2009;339. Available from: <http://www.bmj.com/content/339/bmj.b3723.abstract>
8. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *The Lancet* 373(9678):1874–82.
9. Walsh TS, Salisbury LG, Merriweather JL, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: The recover randomised clinical trial. *JAMA Intern Med* 2015;175(6):901–10.
10. Elliott D, McKinley S, Alison J, et al. Health-related quality of life and physical recovery after a critical illness: a multi-centre randomised controlled trial of a home-based physical rehabilitation program. *Crit Care* 2011;15(3):R142–R142.
11. Denehy L, Skinner EH, Edbrooke L, et al. Exercise rehabilitation for patients with critical illness: a randomised controlled trial with 12 months of follow-up. *Crit Care* 2013;17(4):R156–R156.
12. Jones C, Skirrow P, Griffiths RD, et al. Rehabilitation after critical illness: a randomised, controlled trial. *Crit Care Med* 2003;31(10):2456–61.
13. Connolly B, Salisbury L, O'Neill B, et al. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness. *Cochrane Libr* 2015;



MARS

Van Vught L, Klein Kouwenberg P, Spitoni C, Scicluna B, Wiewel M, Horn J et al. Incidence, Risk Factors and Attributable Mortality of Secondary Infections in the Intensive Care Unit After Admission for Sepsis. JAMA 2016;315(14): 1469-1479

Introduction

ICU-acquired infection is estimated to affect up to 20% of patients admitted to European ICUs.¹ In addition to an increase in morbidity and mortality, length of stay in both ICU and hospital are increased, resulting in an increased cost of care. Environmental factors such as the presence of an endotracheal tube or central venous catheter can predispose to the development of ICU-acquired infection but it has also been recognised that septic patients may undergo down-regulation of the immune response resulting in immunosuppression. This immunosuppression may also contribute to the development of secondary infection.² Epidemiological trials are necessary to improve our knowledge of the incidence and risk factors for ICU-acquired infection. Identification of candidate genetic risk factors for the molecular pathophysiological mechanisms of sepsis and secondary infection may also help to develop future immunomodulatory treatment options for this patient subgroup.

Study synopsis

This prospective, observational association study had three main objectives - to determine in septic patients admitted to the ICU the incidence, risk factors and attributable mortality of ICU-acquired infection. Attributable mortality was defined as the fraction of mortality that can be prevented by elimination of the risk factor i.e. acquired infection. The incidence, clinical risk factors and attributable mortality for ICU-acquired infection in non-septic patients admitted to the ICU was also assessed.

This study was funded as part of the Molecular Diagnosis and Risk Stratification (MARS) project. All patients admitted to 2 tertiary mixed ICUs in The Netherlands between January 2011 and July 2013 and who stayed in ICU for 48 hours or more were eligible for inclusion.

The primary outcome measure was the first occurrence of an ICU-acquired infection. This was defined as any new-onset infection for which a new antibiotic regime was commenced, provided this was at least 48 hours after ICU admission. The likelihood of infection was classified as possible, probable or definite using international consensus definitions.³ The most likely causative microorganism was classified according to all microbiology results. Clinical risk factors for ICU-acquired infection were identified using a multivariable competing risk model. This model provides two measures of association; cause specific hazard ratio (HR) - an estimate of the direct effect of an exposure of



interest (e.g. severity of disease) on a particular outcome (ICU-acquired infection), and the sub-distribution HR - describes the risk of the development of an ICU-acquired infection while accounting for competing events e.g. death, discharge from ICU.

421 patients with a sepsis-related admission to ICU had whole blood taken within 24 hours of admission for genetic profiling. A small number of septic patients (n=28) also had paired samples taken at the onset of an ICU-acquired infection (n=19) and at the onset of a non-infectious ICU complication (9). 42 healthy controls had blood samples taken for genetic analysis and comparison. The purpose of this genetic analysis was to ascertain if the host response to the initial sepsis event differed between those septic patients who developed ICU-acquired infection and those who did not.

Due to baseline differences between groups (medical admissions accounted for 77% vs 48% in septic vs non-septic admissions respectively) septic and non-septic admissions were not compared directly with each other. Instead patients with sepsis on admission who developed a secondary infection were compared with septic patients on admission who did not develop an ICU-acquired infection.

Of 6,994 admissions screened, 3,269 were excluded as they stayed less than 48 hours in the ICU. 85 admissions (69 patients) were excluded as infection was diagnosed between 24 and 48 hours. The final cohort included 3640 admissions of which 1719 (1504 patients) (47.2%), had a sepsis-related diagnosis on admission. The primary outcome measure, the incidence of ICU-acquired infection, occurred in 13.5% of all sepsis related admissions (n= 232) and 15.1% of all non-sepsis related admissions (n= 291).

Baseline exposure to selective decontamination of the digestive tract (SDD), common practice in The Netherlands, did not differ significantly between septic patients who did and did not develop an ICU-acquired infection, 69.8% vs 67.7% respectively. Septic patients who developed ICU-acquired infection were more severely ill, with higher APACHE IV scores (90 [IQR 72-107] vs 79 [IQR 4-9]) (P<0.001), higher SOFA scores (8 [IQR 6-11] vs 7 [IQR 4-9]) (P<0.001) and a higher incidence of shock (104 patients [44.8%] vs 479 patients [32.2%]) (P<0.001). A significantly greater proportion of those that developed an ICU-acquired infection had received steroids prior to the secondary infectious event (70.7% vs 55.7%, P=0.001). 99.1% of septic patients who developed an ICU-acquired infection were mechanically ventilated and 93.5% had a central venous catheter before the diagnosis of secondary infection was made.

Independent risk factors for ICU-acquired infection were respiratory insufficiency as a co-morbid condition (sub-distribution HR 1.44; 95% CI, 1.05 to 2.99), use of a central venous catheter (sub-distribution HR 2.63; 95% CI, 1.53 to 4.53) and mechanical ventilation (sub-distribution HR 6.22; 95% CI, 1.54 to 25.17). Septic patients who developed an ICU-acquired infection had a longer length of ICU stay (22 days IQR, 15 to



33 v 5 days IQR, 3-9, $P < 0.001$) and a higher mortality at day 60, 88 patients (44.2%) vs 381 patients (29.1%), $P < 0.001$), than those septic patients who did not develop an ICU-acquired infection.

The most common ICU-acquired infections, in those admitted with sepsis, were catheter-related blood stream infection ($n=88$, 26.3%), pneumonia ($n=85$, 25.4%) and abdominal infection ($n=53$, 15.9%). Gram-positive bacteria accounted for 45.2% ($n=151$), gram-negative bacteria 26.6% ($n=89$) and fungi 9.6% ($n=32$) of ICU-acquired infection in this group.

There was no difference in admission gene expression profiles between those septic patients who did and did not develop ICU-acquired infection. A difference in admission gene expression profile was present, however, compared to healthy controls. Common pro and anti-inflammatory pathways were overexpressed e.g. toll-like receptors, interleukin 1(IL-1), IL-6, IL-8 and IL-10.

15.1% ($n=291$) of all non-infectious related admissions to ICU were complicated by an ICU-acquired infection. Pneumonia was the most common acquired infection (117 patients, 48.4%). Gram positive and gram negative infections were identified as the causative organism in equal proportions 33.9% v 33.3%, respectively. There was an association between the development of ICU-acquired infection and a higher APACHE IV, a higher SOFA score and shock on admission. Non-infectious related admissions who developed an ICU-acquired infection were also exposed to steroids more often than their counterparts who did not develop an ICU-acquired infection 134 (46%) v 516 (31.3%), $P < 0.001$.

The population attributable mortality fraction of ICU-acquired infection in non-septic admissions was 21.1% (95% CI 0.6%-41.7%) by day 60 compared with 10.9% (95% CI 0.9%-20.6%) by day 60 in patients admitted with sepsis who developed an ICU-acquired infection. When baseline differences are taken into account together with competing risks over time, such as discharge or death, this represents an absolute increase in mortality by day 60 in each group of 2.8% and 2% respectively.

Study critique

This study is to be commended as it is the largest genetic analysis of ICU patients in whom the incidence and features of secondary infection have been researched. As such, it is an important contribution to the literature.

Although internationally recognised definitions were used to identify the likelihood of infection, sepsis and septic shock it must be acknowledged that sepsis is a syndrome, for which there is no single diagnostic test. The early definition of sepsis used in this trial was very non-specific requiring only a suspicion of infection and at least 1 additional

parameter outlined in the 2001 guidelines.⁴ The definition of sepsis has recently been updated and future research in this field will use the 2015 definition perhaps increasing the confidence with which we can identify septic patients.⁵

The invading pathogen in this study was unknown in 24.5% of cases. Biomarkers were not used in this study, but their development may potentially allow increased confidence in the identification of acquired infection. It is likely they will play a central role in future research in this field.⁶ Meticulous clinical phenotyping of patients took place in this study and recognition of the differences in baseline characteristics between septic and non-septic admissions obviated any direct comparisons between these two groups.

Potential confounding variables must be acknowledged e.g genetic expression profiles could be influenced by the specific invading pathogen, by treatment with various drugs and the effect of other organ support modalities. Given the study was carried out in Northern Europe with a low rate of multi-drug resistant pathogens the results may not be generalisable to other less developed countries.⁷ Catheter-related blood stream infection and ventilator associated pneumonia were among the most common ICU-acquired infections with incidences of 4.7% (n=74) and 3.5% (n=54) respectively. The compliance of the 2 units in the study to central line and ventilator bundles of care within their respective institutions is not mentioned.

Another major confounding factor to consider is that during part of this study, both ICUs were involved in a cluster-randomised crossover trial on the effects of SDD (given during 70% of the study) and selective oropharyngeal decontamination(SOD) (given during 30% of the study). Outside the period of this particular study patients received SDD, the standard of care in The Netherlands. Could the host inflammatory response have been influenced by the use of SDD as much as sepsis itself? The results of this study are therefore not applicable to places where SDD is not in widespread use.

The numbers involved in genetic analysis in this study are too small to propose any genetic association. Future studies in this area will require huge databases of hundreds of thousands of patients if we are to untangle and make sense of the vast array of genetic associations which may influence the host response to sepsis.

This study suggests whilst secondary infections are relatively common in ICU, immunosuppression and secondary infection acquired in the ICU is only responsible for a modest contribution to mortality in septic patients, although the wide confidence intervals for the population attributable mortality in both septic and non-septic admissions must be acknowledged.

Where this sits in the body of evidence

In order to determine the prevalence and risk factors of ICU-acquired infection in European ICUs, the EPIC study was completed. 1,417 ICUs in 17 countries contributed

data on 10,038 patient case reports. 2,064 patients (20.6%) had ICU-acquired infection during the 24-hour study period. Pneumonia accounted for >50% of ICU-acquired infection. Severity of illness, length of stay and presence of invasive adjuncts (mechanical ventilation, central venous catheters, urinary catheterisation) were associated with the development of ICU-acquired infection. During a six week follow-up period 1,560 patients (16.8%) died.¹

The EPIC II trial collected epidemiological data from 1,265 ICUs in 75 countries.⁸ This single day point-prevalence study in 2007 indicated that 51% of the 13,796 patients analysed, were infected at that time. Severity of illness and length of stay were again related to the infection rate. Infected patients had an ICU mortality rate of 25.3% v 11% and hospital mortality rate of 33.1% v 15%, compared with non-infected patients. EPICII did not sub-classify infection as community acquired, hospital acquired, ICU acquired as the original EPIC study did.

In order to identify genetic variants that influence survival from sepsis, a genome wide association study of adult white patients admitted to the ICU with sepsis secondary to pneumonia was completed.⁹ The most significant association with 28-day survival was noted to be a single nucleotide polymorphism (SNP) on chromosome 5 in an intron of the FER gene. The FER gene codes for a non-receptor protein tyrosine kinase. It is involved in the regulation of the actin cytoskeleton, chemotaxis, cell adhesion, migration and invasion.

GenOSept is a European collaboration which aims to delineate the genetic influences on the host response and outcomes in sepsis. Data was collected from patients from 102 centres in 17 countries across Europe. An epidemiological survey of those patients admitted with community-acquired pneumonia included 1,166 patients from GenOSept.¹⁰ Mortality rate was 27% at 6 months and independent risk factors for death included APACHE II score (HR,1.03, CI 1.01 to 1.05), bilateral infiltrates on the chest radiograph (HR, 1.44, 95% CI, 1.11 to 1.87) and need for ventilator support (HR, 3.04; 95% CI 1.64 to 5.62).

In a prospective cohort study, transcriptome analysis of peripheral blood leucocytes from 265 adult patients admitted to ICU with sepsis secondary to community acquired pneumonia, defined two distinct sepsis response signatures (SRS1 & SRS2).¹¹ SRS1 was associated with an immunosuppressed phenotype and higher 14 day mortality. Regulatory genetic variants and gene networks identified by this integrated genomics approach identified subgroups of patients with different immune response states and prognoses.

The cytokine response to community-acquired pneumonia and sepsis was studied in 1886 patients in 28 centres in the USA. Subjects were enrolled whilst still in the ED. TNF

and IL-6 were measured as part of the pro-inflammatory and IL-10 as part of the anti-inflammatory cytokine response. Mean cytokine levels were highest on admission and remained elevated throughout the first week. Mortality was highest in those with combined pro and anti-inflammatory activity (HR 20.5, 95% CI 10.8-39.0). The cytokine response was heterogenous with overlap between those who do and do not develop severe sepsis. Only 132 (7%) of this cohort were treated with mechanical ventilation.¹²

How does this trial advance our management of the critical ill patient?

Increased knowledge of the risk factors for, and attributable mortality from, sepsis can aid our decision making in the ICU. Further work will be required to build upon the genetic analysis in this study.

References

1. Vincent J-L, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe: results of the European Prevalence of Infection in Intensive Care (EPIC) Study. *Jama* 1995;274(8):639–644.
2. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol* 2013;13(12):862–874.
3. Calandra T, Cohen J. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. *Crit Care Med* 2005;33(7):1538–1548.
4. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med* 2003;29(4):530–538.
5. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *Jama* 2016;315(8):801–810.
6. Abraham E. New Definitions for Sepsis and Septic Shock: Continuing Evolution but With Much Still to Be Done. *JAMA* 2016;315(8):757–759.
7. Angus DC, Opal S. Immunosuppression and Secondary Infection in Sepsis: Part, Not All, of the Story. *JAMA* 2016;315(14):1457–1459.
8. Vincent J-L, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *Jama* 2009;302(21):2323–2329.
9. Rautanen A, Mills TC, Gordon AC, et al. Genome-wide association study of survival from sepsis due to pneumonia: an observational cohort study. *Lancet Respir Med* 2015;3(1):53–60.
10. Walden AP, Clarke GM, McKechnie S, et al. Patients with community acquired pneumonia admitted to European intensive care units: an epidemiological survey of



the GenOSept cohort. Crit Care 2014;18(2):1.

11. Davenport EE, Burnham KL, Radhakrishnan J, et al. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. Lancet Respir Med 2016;4(4):259–271.
12. Kellum JA, Kong L, Fink MP, et al. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. Arch Intern Med 2007;167(15):1655–1663.

Miscellaneous Trials



REACT-2

Sierink JC, Treskes K, Edwards MJR, Beuker BJA, Hartog D den, Hohmann J, et al. Immediate total-body CT scanning versus conventional imaging and selective CT scanning in patients with severe trauma (REACT-2): a randomised controlled trial. *The Lancet* 2016;388(10045):673-83

Introduction

Each year 12,000 to 16,000 patients are severely injured in the UK.^{1,2} Since 1978, Advanced Trauma Life Support (ATLS) has formed the basis of trauma management in many countries. In ATLS, plain radiographs of the chest, pelvis and C-spine and focussed abdominal sonography in trauma (FAST) scanning were deemed adjuncts to the primary survey, with CT scanning accompanying the secondary survey.³ More recently, Royal College of radiology guidelines stated that total body contrast-enhanced CT is the default imaging technique for seriously injured patients.⁴ Total body CT is now recommended by the National Institute for Health and Care Excellence (NICE) in cases of major trauma, despite a lack of level 1 evidence.⁵ However, identifying seriously injured patients is challenging; major trauma or polytrauma is defined as an injury severity score (ISS) ≥ 16 , but this can only be determined retrospectively. Therefore it is difficult for clinicians to judge who should undergo total body CT scanning. Even the use of triage tools to determine which patients are likely to be seriously injured and require total body CT results in a 30% over-triage rate.⁶

To date, the best evidence on total body CT in polytrauma has come from a retrospective analysis of trauma registry data which demonstrated that total body CT is associated with a decrease in standardised mortality ratio (SMR, 0.745; 95% CI, 0.633 to 0.859).⁷ The potential benefits of total body CT scanning must be weighed up against the risks associated with radiation exposure. In the non-trauma setting, there has been a drive to reduce radiation exposure; newer CT imaging techniques can reduce the dose delivered by 27% to 71%.^{8,9} Therefore, the onus is on the treating clinician to justify the need for radiological examination and radiologists to optimise imaging techniques to deliver radiation doses that are As Low As Reasonably Achievable (ALARA).¹⁰ For these reasons, a prospective randomised controlled trial investigating whether there was a benefit associated with total body CT scanning was needed. The REACT-2 trial set out to address this question and also quantify the radiation exposure associated with whole body CT scanning in trauma.

Study synopsis

This multi-centre, randomised controlled trial compared the effect of total-body CT scanning with standard work-up (conventional radiology supplemented with selective CT scanning) in patients with trauma. The trial was carried out at four level one trauma



centres in the Netherlands and one in Switzerland. Patients were cared for by experienced trauma teams who received feedback on adherence to study procedures within one day of each trauma.

Trauma patients aged ≥ 18 years were screened for eligibility. The authors sought to include the most severely injured patients. As polytrauma is determined retrospectively, the authors set inclusion criteria based on physiological parameters on admission, a suspicion of life threatening injuries or a worrying mechanism of injury (table 8). Patients with low energy blunt trauma, penetrating stab wounds to one body region, those who were moribund or needed immediate surgery were excluded.

| Physiological Parameters | Life Threatening Injuries | Mechanism of Injury |
|---------------------------------------|----------------------------------|-------------------------------|
| Resp Rate ≤ 10 or ≥ 30 /min | ≥ 2 Long Bone Fractures | Fall > 3m in Height |
| Heart Rate ≥ 120 bpm | Severe Rib / Open Chest injuries | Ejection from a Vehicle |
| Systolic BP ≤ 100 mm Hg | Severe Abdominal Injury | Death in Same Vehicle |
| Blood Loss ≥ 500 ml | Pelvic Fracture | Severely Injured Same Vehicle |
| GCS ≤ 13 or abnormal pupil | Unstable Spine or Cord Injury | Trapped Chest / Abdomen |

Table 8: Inclusion criteria

Eligible patients were randomised in the trauma room on a 1:1 basis using a computer programme, there was no blinding of clinicians or patients. Informed consent was initially waived. A primary survey was conducted, during which the following life saving interventions were carried out if indicated; intravenous access, endotracheal intubation, chest tube insertion, pericardiocentesis, and control of haemorrhage. Only then did the patients progress to imaging. The CT scanner was located in the trauma room or in an adjacent room within the emergency department.

Patients in the total-body CT group underwent CT scanning from vertex to pubic symphysis performed using a two step technique; a non-contrast CT of head and neck followed by a CT of chest, abdomen and pelvis using intravenous contrast. Those in the standard work-up group had chest and pelvic x-rays along with a FAST scan as part of a primary survey. A protocol was used to determine body areas requiring targeted CT scanning.

The primary endpoint was in-hospital mortality. There were a large number of secondary endpoints, amongst them were; 24 hour and 30 day mortality, time from arrival to completion of imaging, time from arrival to diagnosis of life-threatening injuries, time in the trauma room, radiation exposure and hospital costs. When calculating the radiation doses for plain radiographs, a dose catalogue was used. Where doses were not available assumptions were made. For CT radiation doses, mean doses were calculated from CT

scans taken at one of the participating centres.

To achieve an 80% power to detect a reduction in mortality from 12% to 7%; 539 patients were required in each group. A two-sided alpha level of 5% was used. Analysis was carried out on a modified intention-to-treat population. A post hoc per-protocol analysis (excluding cross-overs) was performed. Pre-specified subgroup analysis was carried out on patients with polytrauma and those with severe traumatic brain injury (defined as a GCS < 9). Three pre-planned, unmasked interim analyses were carried out for safety.

5,475 patients were assessed for eligibility, 3,860 met exclusion criteria, 212 eligible patients were missed. In total, 1403 patients were randomly assigned to a treatment allocation, 203 of these were subsequently deemed ineligible, 117 declined further participation or had a language barrier that prevented participation. The primary analysis consisted of 541 patients in the total-body CT group and 542 in the standard work-up group. Six cross-overs occurred in the total-body CT group and 18 in the standard work-up group. There were 111 protocol violations.

The groups were well balanced at baseline in relation to mechanism of injury, co-morbidities and physiological parameters. Among the 1083 patients recruited, data on mechanism of injury was available for 1,064; 32% had a fall from height and 55% had a motor vehicle collision. The median ISS was similar between the two groups; 20 in the whole body CT group compared to 19 in the standard work-up group. More patients in the whole body CT group had suffered polytrauma (67%) compared to the standard work-up group (61%).

The in-hospital mortality was 16% in both groups ($P=0.92$). A priori subgroup analysis demonstrated no difference in hospital mortality in patients with polytrauma (total-body CT, 22% vs standard work-up, 25% ($P=0.46$)) or those with traumatic brain injury (38% vs 44% $P=0.31$). There was no difference in mortality at 24 hours or 30 days.

Patients in the total-body CT group had a higher median radiation exposure during their hospital stay (21.0 mSv [IQR, 20.9 to 25.2] vs 20.6 mSv [IQR, 11.8 to 27.6]; $P<0.0001$). In the standard work-up group 45% of patients received a dose of radiation less than 20 mSv; this was the lowest dose received by any patient in the whole body CT group. In the standard work-up group, 46% of patients underwent sequential scanning of all body segments and therefore ultimately had a total-body CT. Patients in the whole body CT group had their imaging completed sooner (median 30 min vs 37 min; $P<0.0001$), and had a quicker time to diagnosis (median 50 min vs 58 min; $P=0.001$). Patients with polytrauma spent less time in the trauma room (69 min vs 82 min; $P=0.011$). There were five deaths during CT scanning, all occurred in elderly patients (median age 81) with seemingly unsurvivable injuries; 3 in the whole body CT group, 1 in the standard work-up group and



1 patient who was excluded after randomisation.

Whole body CT scanning did not result in higher hospital costs overall (mean €24,967 vs €26,995; $P=0.44$), though more in depth cost effectiveness, along with long term outcomes will be published at a later date.

Study critique

This thought provoking study addressed the role of total body CT in trauma in comparison to standard work-up. There were a number of drawbacks. There was no blinding as to treatment allocation. The challenges in accurately assessing injury severity, even in a trauma centre in the context of a clinical trial are demonstrated by the fact that 22.8% of patients were excluded after enrolment, including 14.5% who were enrolled in error.

There was no difference in the primary outcome measure of in-hospital mortality. The lack of difference in mortality must be discussed in the context of a potential Hawthorne effect. Patients were treated in level one trauma centres by experienced trauma teams, which were led by consultants with CT scanners located in the trauma bay or an adjacent room. The investigators argue they aimed to “keep the study as close to daily practice as possible”. However, in the standard work-up group there was an extensive list of criteria to determine which body regions required further CT scanning (the decision to proceed to CT brain was based on a combination of 12 major and 6 minor criteria). This was accompanied by feedback on performance within one working day of each trauma. It would seem unlikely that such practices would be reproduced outside a clinical trial. Ultimately, this was a trial of total body CT compared with heavily protocolised selective CT scanning conducted by experienced trauma teams. This may have improved care in the standard work-up group and helped reduce the number of missed injuries.

The study was powered to detect a reduction in mortality from 12% to 7%. The only conceivable way this 42% relative risk reduction in mortality could have been achieved was if the whole body CT group had much earlier diagnosis of life threatening injuries or there were numerous missed injuries in the standard work-up group. How many CT scans resulted in a change in patient management, or how many patients in the standard work-up group had a delayed diagnosis of a life-threatening injury was not presented. The best surrogate of this is the time to diagnosis, which was only marginally quicker in the total body CT group (50 min vs 58 min; $P=0.001$). Total body CT resulted in a modest reduction in the time to complete scanning (7 minutes) and to exit the trauma bay (9 minutes). The small time differences in completion of scanning may have resulted in the lack of difference in mortality.¹¹ The modest benefits in earlier completion of imaging and time to diagnosis must be weighed up against the excess radiation exposure (0.4 mSv) in the total body CT group.



The total difference in radiation exposure (0.4 mSv) may have limited clinical relevance. Long term follow up of atomic bomb survivors has provided much of the information about the dose response relationship between exposure to radiation in doses 5 - 100 mSv and cancer.¹² There is a lack of reliable evidence for cancer induced by doses of radiation < 1 mSv, this is in the typical range of plain radiographs. 40% of the population will get cancer in their lifetime, this produces such a large confounding variable that it is almost impossible to accurately determine the incidence of cancer induced by small doses of radiation administered in radiological investigations.¹² Hence, it is difficult to accurately represent the cancer risk associated with 0.4 mSv. However, to give the reader perspective; plain radiographs of the thoracic spine deliver 1.0 mSv of radiation and result in 20 cases of cancer per million examinations and one pelvic x-ray delivers 0.6 mSv and causes 30 cases per million examinations.^{13,14} Implementing a total body CT policy for the 12,000 to 16,000 polytrauma victims seen in the UK each year would result in one new case of cancer in the UK approximately every two to three years.^{1,2,13,14} The benefit of reducing administered radiation dose by 0.4 mSv is not zero but in reality may be more than offset by the risk of missed diagnosis of life threatening injuries.¹²

A number of assumptions were made on the radiation dose from plain x-rays, limiting accuracy of the reported doses in the standard work-up group. There were 111 protocol violations within the trial. These resulted in 32 patients in the total body CT group receiving additional radiation. In contrast, 44 patients in the standard work up group received less radiation than their protocol dictated. In the standard work-up group, there were wide interquartile ranges for the total dose of radiation received (20.6 mSv, IQR 11.8 to 27.6 mSv). The authors point out that 45% of patients received a smaller dose of radiation than the lowest dose given to the total body CT group. It follows on logically that the 55% of the standard work-up group received a radiation dose of the same or higher than this. Given the wide IQR we can only deduce that some patients in the standard work-up group received large doses of radiation.

The lack of differences in mortality could also be attributable to a number of other causes. 36% of patients had an ISS < 16 and, by definition, did not have polytrauma. Hypotension was only present in 7% of cases and the pH was 7.34 and 7.35 in the total body CT and standard work-up groups respectively. These less severely injured patients are potentially less likely to benefit from total body CT, thus diluting the treatment effect. The counter argument to this is that there was no significant difference in mortality in the subgroup analysis of patients with polytrauma. This reflects real world clinical practice where patients are often over triaged due to the difficulties in identifying severely injured patients.⁶

In summary, this trial demonstrated no difference in mortality. This may in part be due to the inability to accurately identify polytrauma patients and dilution of the treatment effect, a Hawthorn effect in the standard work-up group or the small time differences in

completion of scanning between the two groups. The authors propose that future work should concentrate on which patient population benefits from total body CT, but given the lack of signal of benefit in any patient group and the challenges in accurately triaging trauma patients, it is hard to know where this research should focus. In light of the potential benefits of whole body CT, the risk of missing life threatening injuries with selective scanning, and the limited evidence of harm with small increases in radiation, it seems likely that many clinicians will continue to follow NICE guidelines and use total body CT scanning in trauma.⁵

Where this sits in the body of evidence

A retrospective multi-centre study of 4,621 polytrauma patients with blunt trauma was carried out to examine the effect of whole-body or non-whole-body CT on survival. Standardised mortality ratios (SMR) were calculated based on the trauma injury severity score (TRISS) and revised injury severity classification (RISC). Using the TRISS model, the SMR of those who had a whole body CT was 0.745 (95% CI, 0.633 to 0.859) compared to 1.023 (95% CI, 0.909 to 1.137) for those who did not ($P < 0.001$). Using the RISC model; SMR were 0.865 (95% CI, 0.774 to 0.956) vs 1.034 (95% CI, 0.959 to 1.109) respectively ($P = 0.017$). Multivariate analysis demonstrated that whole body CT was an independent predictor of survival. The mean time from trauma room admission to CT was 35.5 minutes in the whole body CT group compared to 46.6 minutes in the non whole body CT group ($P < 0.001$).⁷

An observational study of 161 trauma patients looked at time to completion of imaging using either whole body CT as a sole imaging modality or standard work up. The whole body CT group had imaging completed in a median of 23 min (IQR 17 to 33) compared to 70 min (IQR, 56 to 85) in the standard work up group. The definitive management plan was arrived at 47 min (IQR, 37 to 59) and 82 min (IQR, 66 to 110) respectively.¹⁵

A retrospective study of trauma registry data (which was prospectively collected) including 233 polytrauma patients was performed. The body regions scanned were based on the clinical need of each patient. Total body CT was performed in 70 / 233 patients. The median time to acquisition of first CT images was 76 min (IQR 52 to 115) and to completion of final CT image was 93 min (IQR 71 to 129). Performing total body CT did not result in quicker initiation (72 min, $P = 0.13$) or completion (97 min $P = 0.67$) of imaging.¹⁶

A single-centre prospective observational study involving 1000 patients, evaluated the role of whole body CT in patients who had suffered a blunt trauma but had no obvious signs of injury. Patients were enrolled if they had (1) no evidence of chest or abdominal injury, (2) were cardiovascularly stable, (3) had normal abdominal examination results or could not be evaluated due to a depressed level of consciousness and (4) a significant mechanism of injury. Of the 1000 patients; 592 had a normal abdominal examination and



408 had a depressed level of consciousness. The incidence of abnormalities found on CT scanning was as follows; brain 13.9%, C-spine 5.4%, chest 20.9%, abdominal 8.3%. There was no difference in the chance of abnormalities being found on the chest or abdominal CT when the groups who had normal examination and those who were not evaluable due to depressed level of consciousness were compared. CT scanning changed the management of 18.9% of patients.¹⁷

Medicine is now the largest source of ionising radiation in the USA. Using previously published data, Mettler and colleagues tried to create a catalogue of effective radiation doses. Examples included; posteroanterior chest x-ray 0.02 mSv, CT chest 7 mSv, CT abdomen 8 mSv, coronary angiography 18 mSv and pelvic vein embolisation 60 mSv.¹³ It should be noted, imaging technology is evolving at a rapid rate with ever reducing doses of ionisation being used.

A study was carried out to define the cumulative risk of nine cancers, up to age 75 years, attributable to use of diagnostic x-rays. United Nations data from Japanese atomic bomb survivors, along with data on smoking and X-ray exposure in the same population was used to create both relative and absolute risk models. Data from 14 countries was used to determine the frequency of exposure to X-rays. Coronary angiography carried the greatest risk (280 additional cases of cancer per million examinations performed) followed by cerebral angiography (180). CT scanning resulted in 60 additional cases per million examinations performed and chest x-rays resulted in just one.¹⁴

A small study involving 20 polytrauma patients compared continuous protocol scanning from cranial vertex to symphysis pubis with a conventional segmented protocol that imaged cerebral, cervical spine, chest, abdominal, and pelvic regions separately. Continuous scanning produced a 17% reduction in delivered radiation dose ($P < 0.001$).¹⁸

Should we use conventional imaging with selective CT scanning in the management of patients with life-threatening trauma?

Probably not. It seems likely whole body CT will remain the standard of care.

References

1. NECPOD Report. 2007. Trauma Who Cares?
http://www.ncepod.org.uk/2007report2/Downloads/SIP_summary.pdf Accessed 20/12/16.
2. Airey CM, Franks AJ. Major trauma workload within an English Health Region. *Injury*. 1995 Jan;26(1):25–31.
3. Kool DR, Blickman JG. Advanced Trauma Life Support®. ABCDE from a



- radiological point of view. *Emerg Radiol.* 2007 Jul;14(3):135–41.
4. Royal College of Radiology. 2010. Standards of practice and guidance for trauma radiology in severely injured patients. [https://www.rcr.ac.uk/sites/default/files/docs/radiology/pdf/BFCR\(11\)3_trauma.pdf](https://www.rcr.ac.uk/sites/default/files/docs/radiology/pdf/BFCR(11)3_trauma.pdf). Accessed 21/12/16.
 5. National Institute for Health and Care Excellence. 2016. Major trauma: assessment and initial management (NICE guideline 39). www.nice.org.uk/guidance/ng39. Accessed 21/12/16
 6. Wurmb TE, Frühwald P, Hopfner W, Roewer N, Brederlau J. Whole-body multislice computed tomography as the primary and sole diagnostic tool in patients with blunt trauma: searching for its appropriate indication. *The American Journal of Emergency Medicine.* 2007 Nov;25(9):1057–62.
 7. Huber-Wagner S, Lefering R, Qvick L-M, Körner M, Kay MV, Pfeifer K-J, et al. Effect of whole-body CT during trauma resuscitation on survival: a retrospective, multi-centre study. *The Lancet.* 2009 Apr;373(9673):1455–61.
 8. Leipsic J, Nguyen G, Brown J, Sin D, Mayo JR. A Prospective Evaluation of Dose Reduction and Image Quality in Chest CT Using Adaptive Statistical Iterative Reconstruction. *American Journal of Roentgenology.* 2010 Nov 1;195(5):1095–9.
 9. Marin D, Nelson RC, Schindera ST, Richard S, Youngblood RS, Yoshizumi TT, et al. Low-Tube-Voltage, High-Tube-Current Multidetector Abdominal CT: Improved Image Quality and Decreased Radiation Dose with Adaptive Statistical Iterative Reconstruction Algorithm—Initial Clinical Experience. *Radiology.* 2009 Dec 14;254(1):145–53.
 10. McCollough CH, Primak AN, Braun N, Kofler J, Yu L, Christner J. Strategies for Reducing Radiation Dose in CT. *Radiol Clin North Am.* 2009 Jan;47(1):27–40.
 11. Wurmb TE, Bernhard M. Total-body CT for initial diagnosis of severe trauma. *Lancet.* 2016 Aug 13;388(10045):636–8.
 12. Brenner DJ. What we know and what we don't know about cancer risks associated with radiation doses from radiological imaging. *BJR.* 2014 Jan 31;87(1035):20130629.
 13. Mettler FA, Huda W, Yoshizumi TT, Mahesh M. Effective Doses in Radiology and Diagnostic Nuclear Medicine: A Catalog. *Radiology.* 2008 Jul 1;248(1):254–63.
 14. Berrington de Gonzalez A, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. *The Lancet.* 2004 Jan 31;363(9406):345–51.
 15. Wurmb TE, Frühwald P, Hopfner W, Keil T, Kredel M, Brederlau J, et al. Whole-body multislice computed tomography as the first line diagnostic tool in patients with multiple injuries: the focus on time. *J Trauma.* 2009 Mar;66(3):658–65.



16. Easton R, Sisak K, Balogh ZJ. Time to computed tomography scanning for major trauma patients: the Australian reality. *ANZ J Surg.* 2012 Sep;82(9):644–7.
17. Salim A, Sangthong B, Martin M, Brown C, Plurad D, Demetriades D. Whole body imaging in blunt multisystem trauma patients without obvious signs of injury: Results of a prospective study. *Arch Surg.* 2006 May 1;141(5):468–75.
18. Ptak T, Rhea JT, Novelline RA. Radiation Dose is Reduced with a Single-Pass Whole-Body Multi-Detector Row CT Trauma Protocol Compared with a Conventional Segmented Method: Initial Experience. *Radiology.* 2003 Dec 1;229(3):902–5

Early Mobilisation

Schaller S, Anstey M, Blobner M, Edrich T, Grabitz S, Gradwohl-Matis I et al. Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. *Lancet* 2016;388:1377-88

Introduction

As advanced organ support has improved, and ICU mortality has reduced over the last number of decades, there has been an increased recognition of the multidimensional impact of critical illness on patients and their carers. Post-intensive care syndrome (PICS) is the name given to the collection of physical, psychological and cognitive sequelae observed in many ICU survivors.¹

ICU-acquired weakness is a key cause of the physical impairment experienced as part of PICS and impacts not only on length of ICU and hospital stay, but quality of life thereafter.² It is estimated that critically ill adults can lose up to 10% of muscle mass within 1 week.³ Functional disability has been demonstrated up to 5 years after critical illness in survivors of ARDS.⁴ Studies in differing populations of ICU patients have used exercise and mobilisation along with other interventions such as speech and language and dietetic advice to try and ameliorate the often devastating effects of PICS.⁵⁻⁸

Considerable heterogeneity in the methodology of studies, combined with a variety of clinical settings and over 250 different instruments measuring a plethora of primary and secondary outcomes have been used in an effort to try and make sense of the physical, cognitive and psychological impact of PICS on quality of life.^{9,10} The optimum mode, intensity and duration of ICU rehabilitation for survivors of critical illness remains elusive.

Study synopsis

This multi-centre, randomised, controlled trial involved 5 university affiliated ICUs – 3 in the US and 2 in Europe. The study tested whether early, goal-directed mobilisation would improve mobility during the ICU stay, as measured by the Surgical ICU Optimal Mobilisation Score (SOMS), compared to a control group managed in a standard fashion. Patients who were functionally independent at baseline, as measured by the Barthel Index Score, and who were < 48 hours mechanically ventilated but expected to remain so for at least another 24 hours were eligible for inclusion in the study. Patients admitted to hospital more than 5 days prior to screening were excluded as were those with a GCS < 5, post-cardiac arrest patients and those suffering a ruptured or leaking aortic aneurysm. Web-based, block randomisation, stratified by APACHE II (≤ 12 or ≥ 12) and GCS (≤ 8 or ≥ 8), assigned patients in a 1:1 ratio to either intervention or control groups.

The intervention group consisted of two components which commenced within 24 hours



of randomisation:

- Identification of a challenging mobilization goal for the day (Target SOMS Level - Table 9)
- Implementation of this mobilization goal across shifts by the utilisation of an interdisciplinary closed-loop communication strategy.

| Mobilisation Goal (Target SOMS) | Definition of Mobilisation Goal |
|--|--|
| Level 0 | Passive Range of Motion |
| Level 1 | Sitting |
| Level 2 | Standing |
| Level 3 | Ambulation |

Table 9: Mobilisation goal based on the Surgical ICU Optimal Mobilisation Score

An experienced facilitator (physiotherapist, nurse or medical doctor) attended daily ward rounds and encouraged the multidisciplinary team to identify and address any potential barriers to implementation of a target mobilisation goal set by the clinical team. The facilitator devoted 15 minutes per patient per day to the intervention but had no input to the physical mobilisation of the patient – this was carried out by the bedside nurse or a physiotherapist. A sign detailing the agreed target mobility score was posted at the patient’s bedside. Concerns from the clinical team in any aspect of implementation of the mobilisation goal were resolved and changes in the plan could be made so the goal could be met. The facilitator encouraged clear communication between clinical teams and emphasized the mobilisation goal as a key component of handover between day and night shifts. At the end of each day-shift the achieved mobility score was noted and communicated across shifts. The control group was managed according to the standard guidelines for mobilisation and physiotherapy in each participating unit.

Both groups were otherwise managed in the same clinical way according to standard unit protocols for sedation, mechanical ventilation, pain, delirium and enteral nutrition. The primary outcome measure was the mean SOMS level achieved during the ICU stay. The main secondary outcome measures included ICU length of stay (LOS) and the mini-modified functional independence mobility score (mmFIM) at hospital discharge. These three main outcome measures were tested in hierarchical pre-specified order and analysed by intention-to-treat. Other secondary and tertiary outcome measures were analysed in the per-protocol population. Outcome measures were monitored from study day 1 until ICU discharge or death.

The power calculation was based on an assumed SOMS difference of 1 between groups

and a mmFIM score at hospital discharge of 59% in the intervention group vs 35% in the control group. With 80% power ($\alpha=0.05$), at an assumed 11% mortality rate and 11% loss to follow-up rate it was estimated 100 patients were needed in each group.

Of 665 patients assessed for eligibility 30% (n=200) were randomised - 104 to the intervention group and 96 to the control group. Of patients assessed but deemed ineligible for inclusion, 22% (n=103) had been admitted to hospital > 5 days prior to ICU admission. 94% (n=188) of participants in this trial were surgical ICU patients. 53% (n=106) came from either abdominal surgical or trauma surgical admission categories. Groups were well matched at baseline - 63% (n=126) being male with a median (IQR) age of 65 (46-74). The median total time spent on physical mobilisation was 60 (0 – 110) vs 48 (20 – 128) minutes, in the intervention and control groups respectively.

The intervention group achieved the target SOMS level in 89% (n=817) of the 918 study days. The mean SOMS level was 2.2 (1.0) vs 1.5 (0.8) in the intervention vs control groups respectively, between group difference -0.7 (0.4 to 1.0), $P<0.0001$. By ICU discharge 52% (n=52) of the intervention group were ambulant (SOMS level 4) compared to 25% (n=24) of the control group. The intervention group had a significantly shorter ICU LOS compared to the control group, 7 (5-12) days vs 10 (6-15) days respectively (between group difference -3.0, 95% CI, -6.0 to -1.0, $P=0.0054$).

More patients in the intervention group were fully functionally independent at hospital discharge (as indicated by a mmFIM score of 8) compared to the control group, 51% (n=44) v 28% (n=25); OR, 2.6; 95% CI 1.4 to 4.8; $P=0.003$. In-hospital mortality was non-significantly higher in the intervention group than the control group 16% (n=17) vs 8% (n=8) ($P=0.09$). 38% of patients were lost to follow-up with only 88 patients completing the 3 month follow-up in total. No difference between the groups was found in relation to quality of life at 3 months post-discharge as indicated by the 36-Item Short Form Health Survey.

Study critique

This was a study almost exclusively of a surgical ICU population who were fully functionally independent prior to ICU admission and had been in hospital for no longer than 5 days prior to randomisation. It was a highly selected study group and not the most severely ill of ICU study populations - mean APACHE II score of 16 (12 -22), vasopressor-free days of 27 (25-28) vs 26 (24-28) and ventilator-free days of 23 (18 – 25) vs 22.5 (16 – 25) in the intervention and control groups respectively.

Although the numbers of elective vs emergency surgical cases is unclear, the most common reason for mechanical ventilation in this trial was CNS dysfunction - 28% (n=55) of patients in total, followed by impaired fluid homeostasis 21% (n=42). These non-specific terms make it difficult to appreciate the primary reasons for patients remaining



intubated at the end of surgery. There were very few patients with cardiorespiratory and septic pathologies representative of the spectrum of ICU illnesses and therefore results cannot be generalized to more heterogeneous ICU populations.

The cornerstone of this study was the early initiation, communication and delivery of the intervention. In 89% (n= 817) of the 918 study days the target SOMS level was achieved in the intervention group. This was an unblinded trial, which may have led to bias - a sign at the end of the patient's bed stipulating the target SOMS score may have served as motivation for patients and staff in the intervention group.

The primary outcome was assessed by a measure (SOMS score) which was an essential part of the intervention group protocol. With intervention delivery and outcome measurement being inextricably linked it is no surprise that SOMS scores differed between groups. This score was developed by the same group of authors and validated in a surgical ICU population, at a single-centre, who were previously functionally independent and of whom only 32.7% (n=37) were mechanically ventilated.¹¹ The difference of 1 between SOMS levels that the power calculation was based on for this study was not achieved. When SOMS levels ≥ 2 are considered at ICU discharge, numbers are similar with 87% (n=87) vs 79% (n=76) of patients sitting out of bed or better in the intervention v control groups respectively.

The intervention was delivered only during the ICU stay. The two subdomains for the mmFIM score (locomotor and transfer) were the same in both groups at ICU discharge indicating most patients were partially dependent on others for locomotor and transfer activities. The mmFIM scores improved in both groups between ICU discharge and hospital discharge to a median of 8 (4-8) v 5(2-8), indicating that most patients in the intervention group became fully functionally independent by hospital discharge compared to the control group who continued to need some help from others or adaptive equipment for locomotor and transfer activities. The improvement in the intervention group became apparent during a time when the intervention was no longer being delivered. Ward based support post-ICU discharge may have differed between groups and across surgical specialties. Alternatively the intervention group may have been set on a trajectory of continued recovery because of the ICU intervention.

The 3 month follow-up response rate of 40% is disappointing, and although no difference in health-related quality of life at 3 months was elucidated between groups, it is difficult to draw any meaningful conclusions from this aspect of the data.

Where this sits in the body of evidence

120 patients with acute respiratory failure who required mechanical ventilation for at least 4 days were randomised to receive either intensive physiotherapy vs standard care for up to 28 days, in a US based trial involving 5 medical ICUs. Physical function was



measured at 1, 3 and 6 months by the Continuous Scale Physical Functional Performance Test (CS-PFP-10). Despite achieving clear separation of time exposed to physical therapy between groups (408 ± 261 mins vs 86 ± 63 mins, $P < 0.001$) no significant difference in CS-PFP-10 was demonstrated between groups at 1, 3 and 6 months.¹²

In a single-centre US randomised controlled trial, 300 patients suffering acute respiratory failure were randomised to standardised rehabilitation therapy ($n=150$) or usual care ($n=150$). The intervention consisted of passive range of movement, active physical therapy or resistance exercise. Although good separation was achieved between groups in terms of delivery of physical therapy, no difference in the primary outcome of hospital length of stay was demonstrated, 10 (6 – 17) vs 10 (7-16) days, in treatment v control groups respectively.¹³

In a phase II single-centre, parallel group trial, 150 patients were randomised to a physiotherapy program ($n=74$) starting in ICU and continuing at ward level through to the outpatient setting or to standard care ($n=76$). Patients were eligible if they had been in ICU for ≥ 5 days. This was a mixed medical/surgical study population with 55% ($n=83$) remaining on mechanical ventilation by randomisation. No significant difference in the primary outcome measure, the 6 Minute Walk Test was demonstrated at hospital discharge or at the 3, 6 and 12 month follow-up intervals.⁷

A trial involving 104 medical ICU patients at 2 university affiliated ICUs in the US, randomised patients to early physical and occupational therapy during a daily sedation hold or to a daily sedation hold and standard care. Over 80% of patients had acute lung injury and over 50% had sepsis with a mean APACHE II score of 20 vs 19 in the treatment vs control groups respectively. All patients were classified as functionally independent prior to admission. 59% ($n=29$) v 35% ($n=19$), ($P=0.02$) of patients in the intervention group vs the control group achieved functional independence by hospital discharge, defined as the ability to perform 6 activities of daily living and walk independently.⁵

In the largest acute stroke rehabilitation trial ever completed, 2014 patients were randomised to very early mobilisation or standard care in a single blinded, multi-centre, randomised controlled trial. Very early mobilisation was associated with a reduction in the odds of a favourable outcome at 3 months in stroke patients as indicated by the modified Rankin Score. A non-significant increase in mortality at 3 months was also noted in the intervention group – 8% ($n=88$) vs 7% ($n=72$) ($P=0.113$).¹⁴

Should we implement this into our practice?

No. This study was of a highly selected group of surgical patients with good pre-morbid function and results cannot be generalized to other ICU populations. We await further trials.



References

1. Elliott D, Davidson JE, Harvey MA, et al. Exploring the scope of post-intensive care syndrome therapy and care: Engagement of non-critical care providers and survivors in a second stakeholders meeting. *Crit Care Med* 2014;42(12):2518–26.
2. Hermans G, Van Mechelen H, Clerckx B, et al. Acute Outcomes and 1-Year Mortality of Intensive Care Unit-acquired Weakness. A Cohort Study and Propensity-matched Analysis. *Am J Respir Crit Care Med* 2014;190(4):410–20.
3. Puthuchery ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. *Jama* 2013;310(15):1591–600.
4. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364(14):1293–304.
5. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *The Lancet* 373(9678):1874–82.
6. Walsh TS, Salisbury LG, Merriweather JL, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: The recover randomised clinical trial. *JAMA Intern Med* 2015;175(6):901–10.
7. Denehy L, Skinner EH, Edbrooke L, et al. Exercise rehabilitation for patients with critical illness: a randomised controlled trial with 12 months of follow-up. *Crit Care* 2013;17(4):R156–R156.
8. Cuthbertson BH, Rattray J, Campbell MK, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. *BMJ [Internet]* 2009;339. Available from: <http://www.bmj.com/content/339/bmj.b3723.abstract>
9. Goddard SL, Adhikari NK. The Challenging Task of Improving the Recovery of ICU Survivors. *JAMA* 2016;315(24):2671–2.
10. Turnbull AE, Rabiee A, Davis WE, et al. Outcome Measurement in ICU Survivorship Research From 1970 to 2013: A Scoping Review of 425 Publications. *Crit Care Med* 2016;
11. Kasotakis G, Schmidt U, Perry D, et al. The surgical intensive care unit optimal mobility score predicts mortality and length of stay. *Crit Care Med* 2012;40(4):1122–8.
12. Moss M, Nordon-Craft A, Malone D, et al. A randomised trial of an intensive physical therapy program for patients with acute respiratory failure. *Am J Respir Crit Care Med* 2016;193(10):1101–10.
13. Morris PE, Berry MJ, Files DC, et al. Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: a randomised clinical trial. *Jama* 2016;315(24):2694–702.



14. Bernhardt J, Langhorne P, Lindley RI, et al. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet Lond Engl* 2015;386(9988):46–55.

CHECKLIST-ICU

Cavalcanti A, Bozza F, Machado F, Salluh J, Campagnucci V, Vendramin P et al. Effect of a Quality Improvement Intervention With Daily Round Checklists, Goal Setting, and Clinician Prompting on Mortality of Critically Ill Patients: A randomised Clinical Trial by the CHECKLIST-ICU investigators. JAMA 2016;315(14):1480-90

Introduction

Quality Improvement (QI) is an umbrella term for novel attempts to improve health care, many of which attempt to effectively implement current established knowledge in the form of research findings or agreed best practice. Checklists have a key role in achieving this, with advocacy at World Health Organisation level in the operating theatre setting.¹ Their use is prevalent in ICUs but their impact on meaningful patient outcomes is unclear.² This is especially true in middle or lower income countries.³ This trial attempts to use the traditional scientific methodology of a randomised controlled trial to assess the effectiveness of a large-scale QI intervention in this area.

Study synopsis

CHECKLIST-ICU was a 2-phase cluster-randomised controlled trial undertaken in Brazilian ICUs aiming to determine whether a multifaceted quality improvement intervention reduced mortality in critically ill patients.

Phase 1 was an observational study to assess baseline data and the ability of each ICU to effectively collect patient data (30 patients within 6 months). In Phase 2, the successful Phase 1 ICUs were randomised to the QI intervention or usual care. The intervention entailed modifying the daily multi-disciplinary ICU round on weekdays only. Nursing staff read aloud the checklist which comprised: Compliance with measures to prevent health-care associated infections (HCAIs); prophylaxis against venous thrombo-embolism; optimisation of nutrition, sedation and analgesia; compliance with lung-protective ventilation in ARDS; assessment of presence of sepsis and progress towards extubation. The team set and recorded daily patient goals, completion of which was assessed later in the day. Units received training and monthly audit data on their compliance with the intervention, alongside frequent reminder SMS messages. Control ICUs continued their usual care. Each centre supplied ethical approval and consent. ICU's enrolled 40-60 consecutive adult ICU patients after a minimum ICU stay of 48 hours, excluding those with an anticipated imminent death. Units were stratified by baseline mortality. ICU staff and researchers were not blinded, those assessing complications were.

The primary outcome was in-hospital mortality, truncated at 60 days. Secondary outcomes included adherence measures, other clinical outcomes and an assessment of the ICU's safety climate. With 102 ICUs each recruiting 50 patients the study had 90%



power to identify a reduction in hospital mortality from 30% to 24% (6% ARR, 20% RRR) at the 5% significance level. Analyses were by intention-to-treat and adjusted for variances in patient severity using the Simplified Acute Physiology Score-3 (SAPS-3). Standardised Mortality Ratios (SMRs) were used to adjust for differences in performance between individual ICUs. All secondary analyses were exploratory, being pre-specified but not initially adjusted for multiple comparisons.

131 ICUs were included in Phase 1, 118 of which successfully proceeded to Phase 2, with 59 randomised to the intervention and 59 to the control group. Control ICUs were larger and more likely to be academic centres but otherwise well matched. In total 13638 patients were involved in the study, 6,877 in Phase 1 and 6,761 in Phase 2; the primary outcome was unknown in only 3 patients. The intervention period was limited to 6 months, with a median duration of 4.5 months.

Groups in Phase 2 were well matched. Mean age was 59.6 and 48% received mechanical ventilation. The majority of patients were medical, with 15% admitted after elective surgery. Numerically more control patients had a diagnosis of cancer or AIDS. The mean (SD) SAPS-3 admission scores were respectively 51.2 (18) / 54.2 (18) in the intervention /control groups.

The QI intervention was successfully introduced in the intervention group, with the checklist being used on 91% of the intended days and the clinician-prompted daily goals on 89%. There were significantly more multidisciplinary ward rounds in the intervention than control group.

In-hospital mortality in Phase 1 was 32.5% (SAPS3- model predicted 27.1%) and ICU mortality was 25%. Central line-associated infections, ventilator-associated pneumonia and urinary tract infections occurred in 7.4, 4.3 and 10.6 cases per 1,000 patient-days respectively. Those receiving mechanical ventilation did so for a mean (SD) of 8.1 (9.3) days.

There was no significant difference in the primary outcome in Phase 2. In-hospital mortality was 32.9% in the intervention group and 34.8% in the control group (OR, 1.02; 95% CI, 0.82-1.26; P=0.88). There was also no significant difference found in the 8 pre-specified secondary clinical outcomes (including health-care associated infections and length-of-stay metrics).

Six of the 20 the pre-specified exploratory secondary outcomes reached individual statistical significance (achievement tidal volume and sedation targets; reduction in central venous and urinary catheter use; staff perception of safety and teamwork climates) but only the reduction of urinary catheter use remained significant after appropriate correction for multiple comparisons (62.8% vs 74.8% of patient days; RR,



0.86; 95% CI, 0.8 to 0.93; $P < 0.001$).

Study critique

In this large trial the QI intervention was appropriately and selectively applied to the intervention group and the primary endpoint was assessed in virtually all patients. This allows confidence in the authors' conclusion that the QI intervention in their setting did not cause a large (6% ARR) reduction in in-hospital mortality - i.e. This is a successful study which did not identify a significant inter-group difference for the primary outcome. Strengths of the study include its large scale, transparent public funding stream and careful design, such as using the initial phase to exclude ICUs unable to successfully collect quality data. This was a laudable achievement in a middle-income country where the burden of critical illness is high but interventions are less studied³. The authors are to be further praised for choosing a clinically relevant primary outcome rather than a composite of process measures, which may well have given a positive headline result but limited the applicability of the study.

Cluster-randomisation allows testing of changes in how an institution delivers care and has been used in previous large-scale critical care trials.⁴ In this study it was postulated that benefit might occur through a change in the ICU safety climate, which may have benefitted control group patients if randomisation at an individual level had occurred. Baseline differences between units can bias results in cluster-randomised trials;⁵ this study attempted to minimize this by recruiting an adequate number of ICUs, randomizing them by a blinded independent researcher and the statistical adjustment of results. Inter-unit variance was estimated in CHECKLIST-ICU as precise data was unavailable; if the true variance was higher the treatment effect may have been underestimated. The exclusion from randomisation of ICUs unable to complete Phase 1 may have reduced variation, but also selected better performing ICUs, which may have reduced any treatment effect.

There was, however, little evidence of any real beneficial impact from the intervention. The anticipated absolute mortality reduction of 6% was optimistic as the intervention targeted supportive rather than specific disease-modifying care. Of the 8 checklist domains, only one had individual RCT evidence of mortality benefit (reduced tidal volume ventilation in ARDS, with 6 ml/kg rather than 8 ml/kg targeted).⁶ The checklist did not mandate specific actions to identified issues and may not have sufficiently modified physician decision-making. There may have been an inadequate clinical effect on care processes with only a reduction in the use of urinary catheters remaining statistically significant after multiple comparison correction.

The trial hasn't fully excluded a beneficial effect from a similar intervention. The QI tool was only mandated on weekdays, as conceivably overall benefit could have been lost if weekend care was substandard. In order to aid recruitment the funding authority limited



the study to 6 months duration to allow control ICUs access to the (presumed beneficial) QI intervention thereafter. Separation between the intervention and control ICUs may have increased with further time. The high median SMRs seen at enrolment would suggest that future attempts to study and implement QI interventions in this population may be a worthwhile aim.

Where this sits in the body of evidence

The study adds substantially to the body of evidence in this area, due to its use of randomisation, scale and a clinically important outcome measure. These are recurring issues with the published critical care QI literature.

Pronovost et al published a before and after cohort study in Michigan (USA) area hospitals of the rate of catheter-related bloodstream infections (103 ICUs, 375,757 catheter-days).⁷ The QI intervention comprised a 'bundle' of central line related measures (hand hygiene, barrier measures and chlorhexadine use at insertion; avoidance of femoral route and daily consideration of removal) alongside safety culture and daily-goals interventions. Catheter-related infections, as defined by the US National Nosocomial Infections Surveillance System, were significantly reduced to near-zero (mean 1.4 vs 7.0 infections per 1,000 catheter days after 18 months, $P < 0.002$). The study was non-randomised; precluding firm attribution of cause-and-effect and the clinical impact of the intervention was not assessed.

Marsteller et al used cluster-randomisation of ICUs to assess the effect of the above intervention in 45 US faith based hospitals.⁸ Catheter-related infection rates were significantly lower in the intervention group when compared to historical data. The control group ICUs did not measure infection rates for 6 months (in an attempt to minimise any Hawthorne effect) and then introduced the same care bundle. Median infection rates were zero in both groups at this point but the authors used a complex regression model to demonstrate a statistically significant reduction in mean infection rates in the intervention group (1.33 vs 2.16 infections per 1,000 catheter days, adjusted incident ratio 0.19; 95%CI, 0.06 to 0.57; $P = 0.03$). The study suggests some evidence of a treatment-effect of the intervention alongside clear evidence of temporal trends.

Bion et al studied the introduction of the same central line bundle to the UK (215 ICUs, 438,887 catheter-days).⁹ Infection rates were monitored as the intervention was applied sequentially to geographical clusters of ICU. There was an impressive temporal decline in infection rates in adult ICUs (1.48 vs 3.47 infections per 1,000 catheter-days, $P < 0.0001$); however, this was seen to be occurring at a similar rate in ICUs yet to introduce the bundle. In a climate of external scrutiny, ICU-diagnosed infection rates are potentially susceptible to changes in reporting behaviour, questioning their use as a sole outcome measure. This study gives a useful description of the real-world effect of QI interventions.

Dubose et al introduced a Quality Rounds Checklist targeting 22 data in a before-and-after single-centre study in a US surgical ICU.¹⁰ They demonstrated a temporal fall in the rate of diagnosis of ventilator-associated pneumonia (adjusted mean 6.65 fewer per 1,000-patient days; 95% CI, -9.27 to 4.04; P=0.008). There was no significant change in any of the assessed clinical outcomes including mortality and length of stay.

Scales et al introduced and measured adherence to a multifaceted QI intervention into 15 Canadian ICUs, which were randomised into two groups.¹¹ Elements were introduced in a different order in each group and individually assessed against units yet to introduce that measure. Overall, care practices were more likely to be adherent in intervention ICUs which was of borderline statistical significance (summary ratio of ORs 2.79; 95% CI, 1.00 to 7.74; P=0.05). The only individually statistical significant component of the bundle was adherence to the central venous line insertion bundle. Clinical outcomes were not assessed.

Weiss et al studied the effect of physician prompting on checklist effectiveness in a non-randomised single-centre (US medical ICU) cohort study.¹² A separate physician identified missed checklist items on the daily round in 140 ICU patients over 82 days. A separate team looked after the 125 control group patients, with the QI checklist but without prompting. The prompted group had a significantly higher proportion of ventilator-free days, compliance with DVT and stress ulcer prophylaxis and a significantly lower duration of central venous catheters and empirical antibiotics use. Unadjusted mortality (secondary outcome) was reduced in the prompted group, both ICU mortality (6.4% vs 13.6%; P=0.05) and hospital mortality (14% vs 26%; P=0.014); APACHE-IV predicted mortality was similar.

In a major international QI study, Haynes et al prospectively measured outcomes before-and-after the introduction of the World Health Organisation (WHO) safe-surgery checklist.¹ Eight hospitals in 8 countries (4 higher income, 4 lower income) enrolled 3,733 and 3,955 adults in the baseline and post-implementation phases. Sites received training targeted at deficiencies identified in the baseline data collection. The checklist prompted oral consideration of anaesthetic safety, infection prophylaxis, team working and the correct surgical procedure. The primary outcome was death or major complication (as previously defined by the American College of Surgery). Post implementation there were significant falls in complications (7% vs 11%; P<0.001) and overall mortality (0.8% vs 1.5%; P=0.003). This persisted after exclusion of the site with the highest reduction. The largest single effect was in the reduction of surgical site infections. Processes targeted by the intervention all significantly improved after implementation. This study changed international practice.

Following this Urbach et al performed a prospective effectiveness study, comparing the

3 months before (109 341 procedures) and after (106,370 procedures) the introduction of the Canadian version of the WHO safe-surgery checklist to 130 hospitals in Ontario.¹³ Median self-reported compliance with the checklist was 99%. There was no effect on risk-adjusted mortality 0.71% (95% CI, 0.66% to 0.76%) vs 0.65% after introduction (95% CI, 0.60% to 0.70%) (P=0.07) or risk-adjusted complication rate (3.86%; 95% CI, 3.76 to 3.96%) vs 3.82% after introduction (95% CI, 3.71 to 3.92%; P=0.53). There was a clinically insignificant decrease in length of stay (absolute mean difference 0.04 days; P=0.001). There were no improvements seen in unadjusted mortality rates or rates of specific measured complications. This study casts some doubt on the reproducibility of the Haynes paper

Should we implement this into our practice?

Routinely – no. If your unit were not achieving its desired compliance with supportive care this may be one potential solution. Like many Quality Improvement initiatives, doing so may not dramatically change patient outcome.

References

1. Haynes AB, Weiser TG, Berry WR, et al. A Surgical Safety Checklist to Reduce Morbidity and Mortality in a Global Population. *N Engl J Med* 2009;360(5):491–9.
2. Ko HCH, Turner TJ, Finnigan MA. Systematic review of safety checklists for use by medical care teams in acute hospital settings--limited evidence of effectiveness. *BMC Health Serv Res* 2011;11:211.
3. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD. Critical care and the global burden of critical illness in adults. *The Lancet* 2010;376(9749):1339–46.
4. Hillman K, Chen J, Cretikos M, et al. Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial. *Lancet* 2005;365(9477):2091–7.
5. Eldridge S, Ashby D, Bennett C, Wakelin M, Feder G. Internal and external validity of cluster randomised trials: systematic review of recent trials. *BMJ* 2008;336(7649):876–80.
6. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342(18):1301–8.
7. Pronovost P, Needham D, Berenholtz S, et al. An Intervention to Decrease Catheter-Related Bloodstream Infections in the ICU. *N Engl J Med* 2006;355(26):2725–32.
8. Marsteller JA, Sexton JB, Hsu Y-J, et al. A multi-centre, phased, cluster-randomised



controlled trial to reduce central line-associated bloodstream infections in intensive care units*: Crit Care Med 2012;40(11):2933–9.

9. Bion J, Richardson A, Hibbert P, et al. “Matching Michigan”: a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. *BMJ Qual Saf* 2013;22(2):110–23.
10. DuBose J, Teixeira PGR, Inaba K, et al. Measurable Outcomes of Quality Improvement Using a Daily Quality Rounds Checklist: One-Year Analysis in a Trauma Intensive Care Unit With Sustained Ventilator-Associated Pneumonia Reduction: *J Trauma Inj Infect Crit Care* 2010;69(4):855–60.
11. Scales DC. A Multifaceted Intervention for Quality Improvement in a Network of Intensive Care Units: A Cluster randomised Trial. *JAMA* 2011;305(4):363.
12. Weiss CH, Moazed F, McEvoy CA, et al. Prompting Physicians to Address a Daily Checklist and Process of Care and Clinical Outcomes: A Single-Site Study. *Am J Respir Crit Care Med* 2011;184(6):680–6.
13. Urbach DR, Govindarajan A, Saskin R, Wilton AS, Baxter NN. Introduction of Surgical Safety Checklists in Ontario, Canada. *N Engl J Med* 2014;370(11):1029–38.

Surrogate Decision Maker

**White D, Ernecoff N, Buddadhumaruk P, Hong S, Weissfeld L, Curtis R et al
Prevalence of and Factors Related to Discordance About Prognosis Between
Physicians and Surrogate Decision Makers of Critically Ill Patients. JAMA
2016;315(19): 2086-2094**

Introduction

Patients requiring invasive mechanical ventilation are often unable to participate in the decision making process regarding the medical care they receive. Shared decision making, in the ICU context, often requires a surrogate decision maker to participate in these conversations on the patient's behalf. Surrogate decision makers represent the values and wishes of the patient when the benefits and risks of any proposed treatment are discussed. Central to the role of surrogate decision maker is the appreciation and understanding of likely outcomes for any proposed treatment. This process requires complex and delicate communication strategies from the ICU multidisciplinary team.

Differences in perceptions of prognosis can arise between the physician and the surrogate decision maker(s). Overly optimistic expectations held by the surrogate can potentially impede or delay the delivery of high quality end-of-life care to a patient.¹ Recently published guidelines outline institutional mechanisms for the resolution of disagreements between physician and surrogate decision makers when requests for potentially inappropriate treatments are made. In order to help clinicians deal with these complex, often morally distressing discussions hospitals must have the necessary support structures in place for staff.²

The aim of this study was to measure the prevalence of discordance between physician and surrogate prognostic estimates and to explore, qualitatively, the reasons for any difference in beliefs that the surrogate may hold. By determining the factors which contribute to misperceptions and misunderstandings in prognostic estimates, the possibility of interventions designed to improve communication in prognostic estimation may become apparent.

Study synopsis

This was a prospective, mixed-methods (quantitative and qualitative) study involving 4 intensive care units (2 medical-surgical, 1 cardiac and 1 neurological) at The University of California, San Francisco Medical Centre. Patients over the age of 18 who remained mechanically ventilated by day 5 of admission, with an APACHE score > 25 and who lacked capacity were eligible for this study. On the 5th day of mechanical ventilation, physicians and surrogates were asked independently and within 1 hour of each other, to provide prognostic estimates on the patient's chances of surviving the hospital admission using a linear scale from 0 to 100%. The surrogate was also asked to provide a



best guess of what they felt the physician's assessment of prognosis was from 0 – 100%. A prior conversation between physician and surrogate concerning prognosis was not a requirement for inclusion in the study.

Discordance was defined as a difference of $\geq 20\%$ between the physician's prognostic estimate and the surrogate's prognostic estimate (discordance could be classified as overly optimistic or overly pessimistic). A misunderstanding was defined as a difference between the physician's prognostic estimate and the surrogate's best guess of the physician's prognostic estimate. A difference in belief was defined as the difference in the surrogate's prognostic estimate and the surrogate's best guess of the physician's prognostic estimate.

An interviewer blinded to the physician's prognostic estimate then immediately conducted a semi-structured interview with the surrogate in order to further probe and clarify themes which determined the surrogate's perception of prognosis. All interviews were recorded.

A team of 4 investigators used constant comparative methodology to develop a framework of concepts emerging from the interviews which helped to explain the reasons behind any discordance between surrogate's prognostic estimates and what they believed to be the physician's prognostic estimates. A final conceptual coding framework for interviews was agreed. Coding validity was ensured by presenting the preliminary findings to a sample of study participants utilizing an approach called member checking.

Two investigators blinded to participants characteristics and each other's work proceeded to code all interviews using the agreed coding framework. The mean κ statistic of 0.86 showed excellent interrater reliability.

Medical records were retrieved to ascertain the patient's hospital survival and the accuracy of the physician's and surrogates' prognostic estimates were compared.

Based on work from a previous French study,³ to detect a prevalence of physician-surrogate discordance of 50%, assuming 80% power and at a 2-sided α level of 0.05, it was estimated a sample of 229 surrogates would be needed.

174 patients, 229 surrogates and 96 physicians agreed to participate in the study. Baseline demographic and clinical characteristics did not differ between patients enrolled and not enrolled to the study.

Physician-surrogate discordance occurred in 122 of 229 instances (53%; 95% CI, 46.8-59.7%). 43% (n=98) and 10% (n=24) of surrogate prognostic estimates were more optimistic and more pessimistic respectively. Misunderstanding accounted for most



discordance 103/122 (84.4%). 28% (n=65) of discordance was due to a combination of misunderstanding and a difference in belief. 17% (n=38) was due to a difference in belief only. 43% (n=75) of patients died in hospital. Although the surrogates prognostic estimate was better than a random guess, the physician's prognostic estimate was significantly more accurate than the surrogates' (C statistic 0.83 vs 0.74, respectively, 95% CI 0.024-0.163; P = 0.008).

Three key themes emerged from the semi-structured interviews as to why some surrogates held discordant optimistic views;

- Performative optimism – when a surrogate believes that by maintaining an optimistic outlook they may influence the likelihood of a positive outcome for the patient.
- Religion – 69% (n=156) of surrogates rated religion as very or fairly important in their lives compared to 29% (n=28) of physicians.
- Unique attributes possessed by the patient which were unknown to the physician.

Reasons for an overly pessimistic prognostic belief from surrogates included a belief that the physician was intrinsically optimistic, was biased because of an emotional investment in the patient or the physician may not have been aware of the circumstances unique to the patient e.g. poor baseline function.

Study critique

This was a well-planned, complex, prospective study which sought to identify the prevalence and the factors influencing physician-surrogate discordance in prognostic estimation. The results obtained supported the scientific basis of the study. By including only those patients with an APACHE score > 25 who remained mechanically ventilated after 5 days, investigators ensured a cohort with a significant burden of disease - the in-hospital mortality rate was 43%.

This study was conducted in San Francisco, arguably one of the world's most liberal cities, with surrogates from a diverse ethnic and educational background. 66% of surrogates reported a Christian faith compared with 20% of physicians. A higher proportion of physicians had no, an agnostic or an atheist religious persuasion – 32% compared to 20% of surrogates.

9% of physicians declined to take part as there was already a degree of conflict with surrogates (personal communication with lead author, Douglas White). The model of care in this study was one of shared care between the primary treating physician and the ICU doctor and thus it is not possible to generalize results of this study to closed ICUs where care is coordinated by the ICU clinician. Exactly how many intensivists took part in the study is not clear.



80% (n=183) of surrogates reported that a conversation about prognosis had occurred by day 5 of mechanical ventilation and thus it is possible that surrogates prognostic estimates may have been influenced by these conversations either consciously or sub-consciously prior to recruitment. Conversations about prognosis and particular treatment goals may have also been conducted with the bedside nurse, other family members, other patients' family members and/or other members of the multidisciplinary team. In addition, surrogates may have sought external sources for prognostic information e.g. the internet.

The division of reasons for discordance into a binary classification of misunderstanding and differences in belief may be an oversimplification of the complex interactions and influences that surrogates are exposed to during this extremely stressful time in their lives. Anxiety (70%), depression (35%), stress (33%) and lack of understanding of medical information (50%) are all known to effect families of patients admitted to the ICU early in the course of the admission.⁴ Time is needed for the enormity of the situation confronting surrogates to be realised - time to adapt and time to cope. To ask a surrogate to provide a prognostic estimate of hospital survival at day 5 of mechanical ventilation, especially when 20% had no previous conversation regarding prognosis, is ambitious. It is perhaps not surprising to find a rate of discordance of 53% in this context.

It could be argued that prognostication involves more than just a survival estimate. If surrogates were asked to consider quality of life as an outcome rather than merely survival would the level of discordance in prognostication have been any different? Estimates of quality of life would be more difficult to measure however, as defining quality of life would introduce another level of complexity entirely.

The Four Supports Study: Family Support Intervention in Intensive Care Units (NCT01982877), a follow-up study by the same authors, hopes to complete primary data collection by January 2018 (Personal communication). The aim of this randomised controlled trial is to test a multifaceted communication strategy for family members of critically ill patients in order to ascertain if this intervention reduces long-term anxiety and depression in surrogates. Both intervention and control groups will have two 15 minute education sessions about critical illness and mechanical ventilation. In addition, the intervention group will have assigned to it a nurse/social worker who will deliver four levels of support to the family/surrogate decision makers – emotional support, communication support, decision making support and anticipatory grief support. The primary outcome measure in surrogates will be the 6 month HADS and IES scores. This will be an exciting and informative study in the development of therapeutic interventions for the support of families and caregivers of our patients.



Where this fits in the body of evidence?

In an attempt to analyse the content of communication about prognosis in physician-family conferences 51 physician-family meetings were audiotaped. This multi-centre observational study involved 35 physicians, 51 patients and 169 family members. In-hospital mortality for this cohort of patients was 80% (41 of 51). The content of the meetings was coded in order to identify the types of prognostic information discussed. In 96% of family meetings there was discussion about whether to limit/withdraw life-sustaining treatment or to implement a do-not-attempt resuscitation order. Although less than 50% of eligible meetings were audiotaped, factors associated with greater discussion of prognosis included longer duration of the meeting, greater degree of educational attainment by family members, greater degree of conflict between physician-family members and the physician being of white race.⁵

In order to ascertain whether numeric or qualitative statements are more reliable in conveying physician prognostic estimates, 169 surrogates were randomised to view a video of a simulated family discussion of end-of-life care involving a hypothetical incapacitated patient. In one video the prognosis was conveyed numerically and in the other video it was conveyed qualitatively. Surrogates estimation of patient prognosis did not differ significantly, 22% (SD 23%) vs 26% (SD 24%) ($P=0.26$), for those that viewed numeric estimates of patient prognosis and qualitative estimates of prognosis respectively. 47% of surrogates believed the patient's prognosis was better than the physician's prognostic estimate. Greater trust in their loved one's physician and conveying prognostic estimates numerically was associated with less discordance.⁶

Zier et al, 2008 used a hypothetical clinical scenario, with a poor prognosis, to interview surrogate decision makers using a series of open-ended questions. Interviews were recorded and coded to develop a framework of themes emerging from interviews which described surrogates beliefs about physician prognostic estimates. 88% (44 out of 50) of participants doubted the physician's ability to provide accurate prognostic estimates. Despite this high rate of doubt among surrogates, 100% of participants wanted the physician to provide a prognostic estimate even if this meant hearing of a poor prognosis. 29 out of 50 participants valued hearing of a poor prognosis as they felt it would help them prepare for end-of-life care and death.⁷

30 surrogate decision makers were enrolled into a study, the aim of which was to ascertain how they experienced and coped with prognostic information given to them. Patients involved had been in ICU for an average of 10 days. Inpatient mortality was 50%. Participants underwent a qualitative interview during which they were asked about both their experiences of being surrogate decision makers and also any recommendations they had for physicians to help improve the provision of information during these difficult discussions. Surrogates highlighted the requirement for physicians not only to deliver information, but to be cognisant of the complex emotional stressors that



surrogates are under at this time. Enhanced communication skills training for physicians may facilitate the development of true shared-decision making partnerships between physicians and surrogates.⁸

Should we implement this into our practice?

Yes. We should check surrogates' perception of prognosis prior to discussion of goals of care and be willing to explore the reasons for any misunderstanding or differences in belief they hold.

References

1. You JJ, Downar J, Fowler RA, et al. Barriers to goals of care discussions with seriously ill hospitalized patients and their families: a multi-centre survey of clinicians. *JAMA Intern Med* 2015;175(4):549–556.
2. Bosslet GT, Pope TM, Rubenfeld GD, et al. An official ATS/AACN/ACCP/ESICM/SCCM policy statement: responding to requests for potentially inappropriate treatments in intensive care units. *Am J Respir Crit Care Med* 2015;191(11):1318–30.
3. Azoulay E, Chevret S, Leleu G, et al. Half the families of intensive care unit patients experience inadequate communication with physicians. *Crit Care Med* 2000;28(8):3044–3049.
4. Azoulay E, Chaize M, Kentish-Barnes N. Involvement of ICU families in decisions: fine-tuning the partnership. *Ann Intensive Care* 2014;4(1):1.
5. White DB, Engelberg RA, Wenrich MD, Lo B, Curtis JR. Prognostication during physician-family discussions about limiting life support in intensive care units. *Crit Care Med* 2007;35(2):442–448.
6. Lee Char SJ, Evans LR, Malvar GL, White DB. A randomised trial of two methods to disclose prognosis to surrogate decision makers in intensive care units. *Am J Respir Crit Care Med* 2010;182(7):905–909.
7. Zier LS, Burack JH, Micco G, et al. Doubt and belief in physicians' ability to prognosticate during critical illness: the perspective of surrogate decision makers. *Crit Care Med* 2008;36(8):2341.
8. Schenker Y, White DB, Crowley-Matoka M, Dohan D, Tiver GA, Arnold RM. "It Hurts To Know...And It Helps": Exploring How Surrogates in the ICU Cope with Prognostic Information. *J Palliat Med* 2013;16(3):243–9.



PALLIATIVE CARE

Carson SS, Cox CE, Wallenstein S, Hanson LC, Danis M, Tulskey JA, et al. Effect of Palliative Care-Led Meetings for Families of Patients With Chronic Critical Illness. A Randomised Clinical Trial. JAMA 2016;316(1):51–62

Introduction

Chronic critical illness is a clinical syndrome characterized by the need for prolonged mechanical ventilation and accompanied by a number of clinical signs and symptoms such as neuromuscular weakness, loss of lean body mass, cognitive dysfunction and predisposition to secondary infections.

This syndrome is estimated to affect 5 to 10% of mechanically ventilated patients. With a prevalence of over 100,000 patients in the US and an estimated cost of \$20 billion dollars per annum, the 1 year mortality is thought to be around 50%.¹ The effect of chronic critical illness on family and care-givers is increasingly being appreciated. Anxiety and depression are estimated to affect up to 70% and 35% of family members respectively.² If communication with surrogate decision makers about expected outcomes of chronic critical illness is poor, discordance between the clinical team and the family can result and adversely affect treatment.³

Palliative care is specialized care for patients with serious illness. It is a philosophy of care which aims to improve the patient and family experience and quality of life, regardless of treatment outcomes.⁴ Carson et al⁵ recently completed the first randomised controlled trial of palliative care in chronic critical illness and hypothesized more intensive informational and emotional support for families of patients with chronic critical illness, led by palliative care specialists, would reduce symptoms of anxiety and depression among family members compared with the usual information and support provided by the ICU team.

Study synopsis

Patients were enrolled from three tertiary centre medical ICUs and a community hospital medical ICU in the US. Chronic critical illness was defined as requiring at least 7 days of mechanical ventilation uninterrupted for 96 hours or longer and not expected to be weaned or to die within 72 hours.

Eligible patients were identified through discussion with ICU clinicians and screening of ICU records. Those with chronic neuromuscular disease, trauma and burns were excluded. Family members were eligible if they had responsibility for health care decision making for the patient. After enrolment, patients and family members were randomised to the intervention or the control group through a computer-generated, web-based randomisation system with blinding of allocation.



Both the intervention and control groups in this study were supplied with a brochure describing critical illness, both groups could have meetings with the primary ICU team at any time and both groups also had access to the hospital palliative care team if the treating ICU physician felt it was warranted. In addition to these measures, in the intervention group, the family surrogate decision makers held at least two meetings with the support and information team (SIT). This SIT consisted of a palliative care physician and a nurse practitioner separate from the treating clinical team. Other disciplines such as chaplains and social workers could contribute to the SIT if required. The first SIT meeting was held after 7 days of mechanical ventilation, the second meeting took place 10 days later. Additional SIT meetings could be held between these time points if desired.

SIT palliative care clinicians liaised with ICU physicians before scheduled meetings to ascertain information regarding the patient’s clinical condition, prognosis and previous discussions on goals of care. ICU physicians could attend the SIT meetings if desired. Treating ICU physicians were blinded to the structured template of the SIT meetings however, a degree of flexibility in the content of SIT meetings was permitted in order to tailor the meeting according to particular patient and family needs. If the treating ICU physician did not attend the SIT meeting, feedback was provided by the SIT after the meeting.

| Primary Outcome Measure (Among Surrogates) | Main Secondary Outcome Measures (Among Surrogates) |
|---|--|
| Hospital Anxiety and Depression Scale (HADS) symptom score at 90 days | <ul style="list-style-type: none"> • Impact of Event Scale – Revised Score* (IES-R) at 90 days • Discussion of Patient Preferences • Quality of Communication Scale • Family satisfaction in the Intensive Care Unit |

Table 10: Outcome measures

#scored 0 (best) to 42 (worst); *a measure of post-traumatic stress disorder, scored from 0 (best) to 88 (worst).

150 family members in each group were estimated to be required to detect a minimal clinically important difference of 1.5 for mean total HADS score with 90% power and type 1 error of 5%. 1,865 patients were assessed for eligibility. Most were excluded on the basis they were expected to either die or be extubated within the next 72 hours. 256 patients and 365 surrogates were randomised – 130 patients and 184 surrogates to the intervention group, 126 patients and 181 surrogates to the control group.

There were no significant differences between groups in terms of demographics of surrogates. Baseline mean (SD) HADS scores among surrogates were 16.0 (8.1) vs 16.4 (8.4) in the intervention and control groups respectively. Patients in both groups were similarly well matched.

82% of family surrogate decision makers of 116 (89%) patients in the intervention group underwent at least one SIT meeting. Death, discharge, family refusal or inability to participate were the reasons for meetings not occurring. An average of 1.4 SIT meetings per surrogate took place. A mean of 1.9 meetings of surrogates with the treating ICU team occurred in the intervention group separate from the SIT meetings. This was not statistically significantly different from the mean number of meetings that occurred with the treating ICU team in the control group (mean 2.1 meetings). 13% of patients had a formal palliative care consultation in the intervention group, outside the study protocol, compared with 22% in the control group.

Patient prognosis and understanding by family of the patient's values, goals and preferences were discussed in 89% of the first and 81% of the second SIT meetings. Treating ICU physicians attended 8.8% of the first and 3.3% of the second SIT meetings. 85% (n=312) of family surrogate decision makers completed final interviews a median of 105 days after randomisation.

There was no significant difference in the mean adjusted HADS scores at 3 months between the intervention group (12.2) and the control group (11.4); between group difference, 0.8; 95% CI, -0.9 to 2.6; P=0.34). Symptoms of PTSD measured by the IES-R score were significantly higher in the intervention group (25.9) compared with the control group (21.3); between-group difference, 4.60; 95% CI, 0.01 to 9.10; P= 0.0495. More than 90% of surrogate decision makers in both groups reported that discussions relating to patient preferences, regarding medical treatments and procedures took place. Mean scores on the Family Satisfaction in the Intensive Care Unit did not significantly differ between groups 81.1 vs 84.3, for the intervention and control groups respectively (between-group difference, -3.1; 95% CI, -7.3 to 1.0; P= 0.13).

Study critique

This study took place in 4 closed intensive care units in the US. All patients were managed by experienced and dedicated intensivists. The palliative care physicians who participated as part of the SIT team had a mean (SD) of 17 (8) years of experience as physicians and 5.3 (4.8) years as palliative care physicians although their experience of and background in critical care is not clear.

The study question arose from the observation that external palliative care teams were being consulted for ICU patients with chronic critical illness on a case-by-case basis and genuine equipoise existed about this practice. (Personal communication with lead



author, Shannon Carson).

The definition of chronic critical illness needs some discussion. A minimum of 7 days mechanical ventilation was required for inclusion in this trial. The same research group previously suggested that the placement of a tracheostomy tube could be viewed as a useful temporal threshold to define chronic critical illness.¹ Perhaps if this definition was used, recruitment may have been too slow and the numbers needed might not have been acquired. It is unclear how many patients had a tracheostomy at enrolment or indeed necessitated a tracheostomy during the follow-up study period.

In planning the trial, a minimum of 2 SIT meetings were stipulated but a mean of only 1.4 SIT meetings per surrogate was achieved in the intervention group. In addition, both groups had approximately two meetings with the primary treating ICU team outside of the trial protocol. The degree of separation of the two groups is therefore not clear and the true effect of the SIT team in this context is difficult to appreciate. The internal validity of the trial can thus be questioned.

Many closed ICUs, certainly in the UK, will not regularly consult external palliative care services to discuss ongoing ICU care with families of patients and therefore the conduct of and results of this trial may not reflect or indeed be generalized to clinical practice elsewhere.

There are a number of confounding factors in this study. 52% (n=190) of surrogates in this study had a history of anxiety or depression in the past for which they received treatment. The treating team may have been influenced by feedback after the SIT meetings even though most treating clinicians did not attend the SIT meetings.

The primary ICU physician attended only 8.8% of first SIT meetings and 3.3% of second meetings. Was this because the treating clinician was too time pressured to attend these meetings or was it because of a perception that these meetings would not add anything additional to the overall management of the patient and their families? This may have created a perception of discordance in communication with families.

Prior to the SIT meetings the treating clinician filled out a simple form relating to the likely clinical outcome. This was then communicated to the SIT team who may well have communicated this likely outcome as "fact." Clinical predictors of ICU mortality are poor and discordance between ICU physicians and surrogates is common.^{6,7} The palliative care physicians who led the SIT meetings may not have communicated in the same qualitative or quantitative manner in which they were used to in their normal practice. This may have "reduced the dose of the intervention" e.g. in more than 50% of SIT meetings, alternatives to ongoing ICU care were not discussed. This may or may not have been appropriate. It is questionable whether external palliative care clinicians are best placed

to discuss these issues in the context of an ICU patient.

Was the primary outcome measure of mean HADS score the appropriate measure given the intervention? If an intervention such as the SIT team is studied, and measure of anxiety/depression as a primary outcome is used in surrogates, would a psychologist perhaps be better placed to lead these conversations with surrogates? The high satisfaction scores given by surrogate decision makers for the conduct of the care, emotional support and communication with primary ICU teams may mean that family meetings with an external team are of no additional benefit compared to those conducted with the primary ICU team.

Where this sits in the body of evidence

End-of-life practices were studied in 37 ICUs in 17 European countries, in a prospective multi-centre observational study – The ETHICUS study.⁸ Of 31,417 patients admitted to ICU, 4,248 (13.5%) patients died or had limitations of treatment placed. Limitations were associated with patient age, co-morbidities, diagnosis, geographic variation and religious factors. ETHICUS-2 is now recruiting - a worldwide study collecting data on end-of-life care, in a prospective manner which will reflect the practice changes in this area of intensive care over the last 16 years.

In an effort to obtain world-wide consensus on issues surrounding end-of-life practices in critical care, the WELPICUS study used a modified Delphi process to develop 22 key issues in end-of-life care.⁹ Eventual consensus was obtained for 77 (95%) of the 81 definitions and statements. These consensus statements provide standards of practice for end-of-life care.

Family and surrogate decision makers of 126 patients who were expected to die were recruited in a randomised controlled trial involving 22 medical and surgical ICUs in France.¹⁰ The intervention group was assigned to a proactive family meeting and issued with a written brochure on bereavement. The control group was subject to the usual practices/discussions at the end of life for the ICU in which the patient was being looked after. The primary outcome measure was the 90 day score on the IERS, reflecting the presence or absence of PTSD. The intervention group had longer meetings (30 mins vs 20mins, $P < 0.001$) and the family decision makers spent more of the time talking than the control group (15mins vs 5mins). On day 90 the intervention group had a significantly lower median IERS score than the control group (27 v 39, $P = 0.02$).

In a randomised controlled trial at two hospitals a communication facilitator in the intervention group was used to support communication between physicians and surrogate decision makers, mediate conflict and adapt communication to family needs. There was no difference in anxiety, depression or PTSD at 3 months. At 6 months, there was no difference in anxiety or PTSD but depressive symptoms were lower in the



intervention group (P=0.017).¹¹

Should we implement this into our practice?

No. There is no evidence for improved psychological outcomes among family members, through the use of an external palliative care team in addition to routine ICU led care.

References

1. Nelson JE, Cox CE, Hope AA, Carson SS. Chronic Critical Illness. *Am J Respir Crit Care Med* 2010;182(4):446–54.
2. Azoulay E, Chaize M, Kentish-Barnes N. Involvement of ICU families in decisions: fine-tuning the partnership. *Ann Intensive Care* 2014;4(1):1.
3. Nelson JE, Kinjo K, Meier DE, Ahmad K, Morrison RS. When critical illness becomes chronic: informational needs of patients and families. *J Crit Care* 2005;20(1):79–89.
4. Kelley AS, Morrison RS. Palliative care for the seriously ill. *N Engl J Med* 2015;373(8):747–55.
5. Carson SS, Cox CE, Wallenstein S, et al. Effect of palliative care–led meetings for families of patients with chronic critical illness: A randomised clinical trial. *JAMA* 2016;316(1):51–62.
6. Rucker G, Cook D, Sjøkvist P, et al. Clinician predictions of intensive care unit mortality. *Crit Care Med* 2004;32(5):1149–54.
7. White DB, Engelberg RA, Wenrich MD, Lo B, Curtis JR. Prognostication during physician-family discussions about limiting life support in intensive care units. *Crit Care Med* 2007;35(2):442–448.
8. Sprung CL, Cohen SL, Sjøkvist P, et al. End-of-life practices in european intensive care units: The ethicus study. *JAMA* 2003;290(6):790–7.
9. Sprung CL, Truog RD, Curtis JR, et al. Seeking Worldwide Professional Consensus on the Principles of End-of-Life Care for the Critically Ill. The Consensus for Worldwide End-of-Life Practice for Patients in Intensive Care Units (WELPICUS) Study. *Am J Respir Crit Care Med* 2014;190(8):855–66.
10. Lautrette A, Darmon M, Megarbane, et al. A Communication Strategy and Brochure for Relatives of Patients Dying in the ICU. *N Engl J Med* 2007;356(5):469–78.
11. Curtis JR, Treece PD, Nielsen EL, et al. randomised Trial of Communication Facilitators to Reduce Family Distress and Intensity of End-of-Life Care. *Am J Respir Crit Care Med* 2015;193(2):154–62.



Section 2



The Best of the Rest



The Best of the Rest: NEURO

ATACH-2

Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, et al. Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage. *N Engl J Med* 2016;375:1033-1043

The international ATACH-2 randomised controlled trial compared a lower systolic blood pressure target of 110 to 139 mm Hg with a standard target of 140 to 179 mm Hg in 1,000 patients with haemorrhagic stroke. Adult patients aged ≥ 18 years, with a spontaneous supratentorial intracerebral haemorrhage with a volume $<60 \text{ cm}^3$ and a Glasgow Coma Scale score of between 5 and 15 at the time of presentation to the emergency department, were considered eligible if they had at least one episode of systolic blood pressure > 180 mm Hg between symptom onset and 4.5 hours.

Groups were similar at baseline, with patients having a mean age of 61.9 years and a mean systolic blood pressure of 200.6 ± 27.0 mm Hg. Both groups were randomised at approximately 183 minutes post symptom onset. Intravenous nicardipine was the first-line agent used to lower blood pressure in a protocolised manner, followed by IV labetalol, or diltiazam or urapidil where labetalol was unavailable.

Target blood pressure targets were met in 87.8% of the intensively treated group and 99.2% of the standard group. The trial was stopped early for futility, with no difference in the primary outcome of death or disability (intensive group 38.7% vs control 37.7%; RR 1.02; 95% CI, 0.83 to 1.25; $P=0.84$). There was also no difference in haematoma expansion (18.9% vs 24.4%, respectively; RR 0.78; 95% CI, 0.59 to 1.04; $P=0.09$), treatment related serious adverse events (1.6% vs 1.2%; RR 1.33; 95% CI, 0.46 to 3.84; $P=0.59$) or hypotension (1.2% vs 0.6%; RR 2.00; 95% CI, 0.50 to 8.00).

Should we lower blood pressure in haemorrhagic stroke?

Not on the basis of ATACH-2, although this is just one of several trials in the field, including ICH-ADAPT, ATACH, INTERACT, & INTERACT2. Currently, both European and American guidelines recommend lowering systolic blood pressure to <140 mm Hg within 6 hours of stroke onset.



DahLIA

Reade MC, Eastwood GM, Bellomo R, Bailey M, Bersten A, Delaney A, et al. Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium. A Randomized Clinical Trial. JAMA. 2016;315(14):1460-1468

The DahLIA study (Dexmedetomidine to Lessen ICU Agitation) was a multi-centre, blinded, parallel-group, randomized controlled trial which took place in 15 ICUs in Australia and New Zealand between 2011 and 2013. The aim of the study was to evaluate the α_2 agonist dexmedetomidine as a treatment for agitated delirium in critically ill mechanically ventilated patients.

Eligible patients were adults with agitated delirium requiring significant sedation preventing liberation from invasive mechanical ventilation. Specific exclusion criteria included advanced dementia, head injury and current receipt of an α_2 agonist. Patients were randomised to receive either dexmedetomidine, commenced at a dose of 0.5 $\mu\text{g}/\text{kg}/\text{h}$, and titrated between 0 and 1.5 $\mu\text{g}/\text{kg}/\text{h}$ to achieve a Richmond Agitation-Sedation Scale score of 0 or to achieve physician-prescribed goals, or placebo in a matching syringe. The study drug was to run for a maximum of 7 days. All other care was at the discretion of the treating clinician.

21,500 patients were screened and 74 patients were randomised. Reasons for exclusion were not recorded. Two patients withdrew consent and 1 was enrolled in error. Groups were broadly similar at baseline, with some notable imbalances, including a longer duration of ventilation prior to enrolment in the dexmedetomidine group (63 vs 43 hours). The median patient age was 57 years and over 70% were male. Almost all patients were sedated with propofol, one required mechanical restraint and 20% were receiving an antipsychotic agent. Patients in the control group received greater volumes of placebo and doses of antipsychotics. Dexmedetomidine increased ventilator-free hours at 7 days compared with placebo (median, 144.8 hours vs 127.5 hours, median difference between groups, 17.0 hours; 95% CI, 4.0 to 33.2 hours; $P=0.01$). A number of secondary endpoints also suggested benefit with dexmedetomidine, including accelerated resolution of delirium (23.3 hours vs 40.0 hours; median difference, 16.0 hours; 95% CI, 3.0 to 28.0 hours; $P=0.01$), and time to extubation (21.9 hours vs 44.3 hours; median difference -19.5 hours; 95% CI, -31.1 to -5.3 hours; $P<0.001$).

Should we routinely use dexmedetomidine in the management of agitated delirium in mechanically ventilated patients?

Probably, although larger randomised controlled trials are required to replicate this finding.



SEGA

Jabaudon M, Boucher P, Imhoff E, Chabanne R, Faure JS, Roszyk L, et al. Sevoflurane for Sedation in ARDS: A randomised Controlled Pilot Study. Am J Respir Crit Care Med 2016;epublished September 9th

The SEGA trial was a single-centre, open-label, parallel group, randomised controlled trial, comparing sevoflurane sedation with midazolam sedation in 50 patients within 24 hours of the onset of moderate-to-severe ARDS. The rationale for this trial was that the volatile agent has anti-inflammatory effects which may lessen lung injury and improve gas exchange.

Significant exclusion criteria were intra-cranial hypertension and very low tidal volumes (below 250 ml). Sevoflurane was administered via an AnaConDa device with gas scavenging, and was commenced at 6 ml/min initially and modified every 15 minutes as necessary. Midazolam was started at 0.15 mg/kg/hr and modified hourly as required. Both groups received remifentanyl and cisatracurium infusions, targeting a deep sedation (Richmond Agitation-Sedation Scale 5), with depth of anaesthesia titrated to a bispectral index of 40 to 50. Both groups also received full neuromuscular blockade (train-of-four = 0), and standard lung protective ventilation. The intervention lasted for 24 hours. The primary outcome was PaO₂/FiO₂ on day 2, with secondary outcomes of cellular injury providing mechanistic insights into sevoflurane-induced lung protection.

202 patients were screened and 50 randomised, 25 to each group, with groups being largely similar at baseline. Starting PaO₂/ FiO₂ values were similar; sevoflurane group, 111±37 vs 117±45 in the midazolam group, P=0.8. Pneumonia was the most common cause of ARDS. Mean (±SD) PaO₂/ FiO₂ was significantly higher in the sevoflurane group at day 2 (205±56 mm Hg vs 166±59 mm Hg; P=0.04) and day 3. Additionally, the increase in oxygenation from day 1 to day 2 was also larger with the volatile agent (95±61 mm Hg vs 50±73 mm Hg; P=0.02). These gains in oxygenation were lost at day 4. Various pro-inflammatory and alveolar epithelial injury biomarkers were also reduced in the sevoflurane group, when measured in both plasma and bronchoalveolar lavage on day 2.

There were no differences in clinical course for the rest of the patients stay in ICU, including need for recruitment manoeuvres, proning, inhaled nitric oxide use or mortality.

Should we use sevoflurane sedation as standard in the ICU?

Not yet. Further trials will be required to replicate this work, and provide more patient-centred outcomes.



PremaTOR

Scale D, Golan E, Pinto R, Brooks S, Chapman M, Dale C et al. Improving Appropriate Neurologic Prognostication after Cardiac Arrest. A Stepped Wedge Cluster randomised Controlled Trial. Am J Respir Crit Care Med 2016;194(9):1083-1091

An expected outcome which follows a clinical decision is a powerful reinforcer of an individual's understanding of that disease process. After out-of-hospital cardiac arrest (OHCA) a premature withdrawal of life-sustaining treatment (WLST) in a semi-comatose patient may well become a self-fulfilling prophecy. Current guidelines emphasise the false positive rates of early clinical assessments and complementary tests and advise against WLST before 72 hours.¹ This study aimed to improve compliance with this.

The intervention was applied at hospital-level and included education, site leads, a clinical pathway, reminders and audit / feedback. Hospitals were randomised in clusters to commence the intervention sequentially, with those yet to start acting as the controls. Patients were identified from a Canadian OHCA registry; those comatose, stable, admitted to ICU, not progressing to brain death and without an initial plan to WLST were included. Prognostication was appropriate (primary outcome) if made after 72 hours and based on set criteria (absent pupillary / corneal reflexes, GCS M1-2, bilateral absent Somatosensory Evoked Potentials (SSEPs)). Analyses were adjusted for baseline risk.

905 eligible patients from 18 hospitals over 3 years were included. There was a moderate increase in appropriate prognostication (74% vs 68%; OR, 1.79; 95% CI, 1.01 to 3.19; P=0.05) with the intervention, but deaths after WLST within 72 h did not improve (46% vs 52%; P=0.22) and median time from hospital admission to death did not increase (87 h vs 69 hours; P=0.15). There was no improvement in clinical outcomes (survival with good neurological outcome 43% vs 28%; P=0.19), perhaps due to inadequate application, control hospital behaviour change or too soft criteria. Full sedation clearance wasn't mandated and WLST on basis of poor GCS motor score alone was allowed.

Should we introduce this prognostication bundle to our ICUs?

No. But we should look at how we prognosticate on patients following OHCA.

1. Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the ERC and the ESICM. Resuscitation 2014;85: 1779–1789.



PATCH

Baharoglu MI, Cordonnier C, Salman RAS, de Gans K, Koopman MK, Brand A, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial (PATCH Trial). *Lancet* 2016;387(10038):2605-2613

The PATCH trial was a large, multi-centre, open-label, assessor-blinded, randomised trial in 60 hospitals in the Netherlands, France and the UK, examining the efficacy of platelet transfusion in patients with spontaneous intracerebral haemorrhage associated with anti-platelet medication use.

Eligible patients had suffered a supratentorial haemorrhage within the preceding six hours, a Glasgow Coma Scale score of eight or above, taken anti-platelet agents within the past week and been previously relatively well {modified Rankin Score (mRS) of 0 or 1}. Selected exclusion criteria were planned surgical haematoma evacuation, subdural haematoma, AV malformation, coagulopathy and thrombocytopenia. Patients were randomised in a 1:1 fashion, stratified by centre. Platelet transfusion was to be administered within 90 minutes of brain imaging. The original sample size of 190 provided 80% power at a two-sided 5% significance level to detect a 20% absolute reduction in the primary outcome of death or dependency (defined as mRS 4–6) from 70% to 50%, although the primary outcome was later changed to the shift of each category in the entire range of the mRS at three months.

190 patients were enrolled and randomised, 97 to platelet transfusion and 93 to standard care. 19% of patients had at least one exclusion criteria. Groups were similar at baseline, with the exception of more patients in the transfusion group having peripheral vascular disease (16% vs 4%). Most patients received aspirin. Four patients in the interventional group did not receive platelets while two in the standard care arm did.

Patients in the transfusion group had a worse outcome, with a higher odds of a shift towards death or dependence (crude common OR 1.84, 95% CI, 1.10 to 3.08; $P=0.0200$; adjusted common OR 2.05, 95% CI, 1.18 to 3.56; $P=0.0114$). 42% of the interventional group suffered a serious adverse event, compared with 29% of the control group (OR 1.79, 95% CI, 0.98 to 3.27). No signal of benefit was identified.

Should we routinely use platelet transfusions in patients with haemorrhagic stroke in the setting of anti-platelet therapy?

Possibly. Although PATCH suggests worse outcomes with platelet transfusion, there are issues with the trial methodology which lower confidence in the result.



The Best of the Rest: CIRCULATORY

Chest Compression Rates

Hwang SO, Cha KC, Kim K, Jo YH, Chung SP, You JS et al. A Randomised Controlled Trial of Compression Rates during Cardiopulmonary Resuscitation. J Korean Med Sci 2016;31:1491-1498

In the first multi-centre randomised controlled trial to test the efficacy of two different chest compression rates, 470 patients who had suffered a non-traumatic out-of-hospital cardiac arrest were randomised to CPR with a compression rate of 120/minute (intervention group) vs 100/minute (control group) upon arrival to one of 12 university-affiliated emergency departments in Korea.

The primary outcome measure was sustained (> 20 consecutive minutes) restoration of spontaneous circulation (ROSC). Hospital survival and one month survival with good functional status, as indicated by the Cerebral Performance Category (CPC) were among the secondary outcomes.

After exclusions, 292 patients were included in the final analysis (156 in the intervention group and 136 in the control group). Both groups were well matched at baseline. Mean (SD) times from collapse to arrival at the Emergency Department were 23 (9) minutes vs 25 (12) minutes in intervention and control groups, respectively. Median (IQR) compression rates were 118 (114 to 120) vs 101 (100 to 104), respectively. 42.9% (n=63) vs 50.7% (n=69) of patients achieved sustained ROSC, respectively (difference 7.8%; 95% CI, -3.7 to 19.2; P=0.183). The numbers recruited were less than the 182 in each group the power calculation determined was required to detect a 10% increase in the rate of ROSC in the treatment group, with a power of 80% at the 5% significance level. Secondary outcomes did not differ between groups.

Should we implement this into our practice?

No. This study neither identified a signal of benefit nor was adequately powered to answer the study question. We await future trials.



HYPRESS

Keh D, Trips E, Marx G, Wirtz SP, Abduljawwad E, Bercker S, et al. Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis. The HYPRESS Randomized Clinical Trial. JAMA. 2016;316(17):1775-1785

Current consensus holds that steroids probably reduce the duration of vasopressor-dependent shock but without a certain effect on mortality and with concern regarding side-effects. Following prior successful trials with steroids in pneumonia, the HYPRESS trial investigated whether hydrocortisone may prevent progression to shock in septic ICU patients.

This double-blind, randomised controlled trial was conducted in 34 German ICUs over 5 years. Eligible patients were adults with clinical evidence of infection for <48 hours, at least 2 Systemic Inflammatory Response Syndrome criteria and evidence of organ dysfunction, but not septic shock {hypotension despite 'adequate' fluid resuscitation (CVP or ScVO₂ guided) or vasopressor requirement.} 380 of 9,953 screened patients were randomised equally to hydrocortisone (50mg bolus, 200 mg/day infusion for 5 days then 100 mg/day for 2 days) or matching saline placebo. Main exclusion reasons were shock presence, sepsis >48 hours, prior / current steroid therapy and lack of consent. 27 patients were excluded from the intention-to-treat analysis for consent issues or development of shock before the study drug was given. 24 discontinued the study infusion, and 18 were lost to 180-day follow-up.

Baseline criteria were comparable. Mean age was 65, mean APACHE II score was 19.0, 45% had pneumonia, 25% urosepsis and 21% intra-abdominal sepsis. 6.5% had received etomidate. There was no difference in progression to septic shock (primary endpoint, placebo vs intervention, 22.9% vs. 21.2%; P=0.70). There was no difference in any of 15 reported secondary endpoints including 90 day mortality (16.7% vs 19.9%; P=0.44) except for reduced delirium with hydrocortisone (11% vs 25%; P=0.01). Hyperglycaemia was more common with steroids (91% vs 82%; P=0.01). Results did not differ in the 69/206 patients who had adrenal dysfunction diagnosed on corticotrophin testing. 10% in each group received open-label steroids potentially diminishing group separation.

Should we give hydrocortisone to prevent progression to septic shock?

No. This study did not show evidence of benefit, and the reduction in delirium incidence should be seen as hypothesis generating only. The drop-out rate was high.



Corticosteroid Therapy in Refractory Shock Following Cardiac Arrest

Donnino MW, Andersen LW, Berg KM, Chase M, Sherwin R, Smithline H, et al. Corticosteroid therapy in refractory shock following cardiac arrest: a randomized, double-blind, placebo-controlled, trial. Critical Care 2016;20:82

Donnino and colleagues undertook a tri-centre, parallel-group, blinded, randomised, placebo-controlled trial examining the effects of corticosteroids on post-cardiac arrest shock. Patients were eligible if they were aged over 18 years, had been resuscitated from a cardiac arrest and required vasopressor support for at least one hour post-cardiac arrest. Patients chronically receiving steroids, were requiring vasopressors pre-cardiac arrest or had another indication for steroids were excluded.

Randomisation was performed in a 1:1 fashion. The steroid group received intravenous placebo or hydrocortisone 100 mg every 8 hours for a total of 7 days or until 24 hours after shock reversal. Patients underwent an adrenocorticotrophic hormone stimulation test prior to the administration of the study drug.

50 patients were randomised, 25 into each group, with 48 coming from a single centre. The mean patient age was 69 years, 66% were male, 76% suffered an out-of-hospital cardiac arrest and 68% died in hospital. Groups were matched at baseline, with the exceptions of there being more patients with hypertension in the placebo group and more patients with renal disease in the steroid group. All patients received their course of steroids and no patients were lost to follow-up.

There was no difference in time to shock reversal (primary outcome; HR, 0.83; 95 % CI, 0.40 to 1.75; P=0.63), shock reversal (steroid group, 52% vs placebo, 60%, P=0.78), good neurological outcome (24% vs 32%; P=0.75) or survival to discharge (28% vs 36%; P=0.76.) Nine patients had absolute cortisol deficiency, with no difference in outcomes between groups. Twenty-one patients had relative adrenal insufficiency, again with no difference in outcomes between the groups. The white cell count was higher in the steroid group. No adverse effects were seen.

Should we routinely give steroids to patients with post cardiac arrest shock?

No, this trial does not support this intervention, although absolute numbers were small.



OVATION

Lamontagne F, O'Meade M, Hébert P, Asfar P, Lauzier F, Seely A. Higher versus lower blood pressure targets for vasopressor therapy in shock: a multi-centre pilot randomised controlled trial. (OVATION). Intensive Care Med 2016;42(4):542-550

Despite their ubiquitous presence in sepsis guidelines and clinical practice much uncertainty remains as to the best clinical target for vasopressors in septic shock. They are routinely titrated against a target mean arterial pressure (MAP), balancing driving pressure against vasoconstriction and flow compromise. A 2014 study demonstrated similar mortality when 776 adults were randomised to a MAP target of 80 to 85 mm Hg vs 65 to 70 mm Hg.¹ However, concern existed about an excess of atrial fibrillation (AF) in the high target group and excess of renal replacement therapy in hypertensives randomised to the lower target. This pilot study sought to establish the feasibility of a further large trial in this area.

Eleven US / Canadian centres randomised 118 adults with septic shock to a low vs high MAP target (60 to 65 mm Hg vs 75 to 80 mm Hg), with other ICU care at clinician discretion. Noradrenaline was used in 92%. The low MAP group had a moderate excess of chronic hypertensives (57% vs 33%). The 9 mm Hg achieved separation in mean MAP (79 vs 70 mm Hg) exceeded the preset threshold for future study feasibility. There was no difference seen in overall fluid balance, daily urine output or use of steroids or inotropes. MAP targets were frequently exceeded. The higher MAP target group received more blood transfusions (71% vs 49%; P=0.024), and a non-significantly higher rate of cardiac arrhythmias (36% vs 20%; P=0.07). 28 day mortality overall was 30% and didn't differ between groups. The investigators comment on the lack of evidence-based alternatives to a MAP-targeted vasopressor strategy, with little evidence for protocolised goal-directed targeting of perfusion targets or purely individualised care.

Should we implement this into our practice?

No. This is a pilot study and should be treated as such. There is ample opportunity for further research in this area.

1. Asfar P, Meziani F, Hamel JF et al (2014) High versus low blood pressure targets in patients with septic shock. N Engl J Med 2014; 370:1583-1593



Prophylactic Antibiotics after Out-of-Hospital Cardiac Arrest

Ribaric. Prophylactic versus clinically-driven antibiotics in comatose survivors of out-of-hospital cardiac arrest-A randomised pilot study. Resuscitation 2017;111:103-109

The phenomenon of post-resuscitation systemic inflammatory response in survivors of cardiac arrest is well described and linked to poor outcomes. Attempts have been made to modify this with therapeutic hypothermia, sedation and targeted oxygen therapy with varied success. Concern remains that early respiratory infection may contribute to this clinical picture but be unrecognised and under-treated. Retrospective data suggest a possible benefit of early antibiotics with an association seen with reduced rates of pneumonia and improved survival. This question was prospectively examined in this study.

Consecutive comatose ventilated patients admitted to the ICU in Ljubjana, Slovenia, following out-of-hospital cardiac arrest (OHCA) were screened. 83 of 103 screened were enrolled over 18 months. Patients had a bronchoscopy and microbiological sampling on admission; the 23 with visible tracheal contamination were given empirical antibiotics and followed up separately, the remaining 60 patients were randomised to prophylactic co-amoxiclav or clinically-driven antibiotics (control). Baseline characteristics were well matched: 87% had an initial shockable rhythm, 82% received immediate coronary angiography and all received therapeutic hypothermia (32 to 34°C).

Antibiotic use in the control group had reached over 80% by day 6, by day 7 chest X-rays showed signs of pneumonia in 50% of each group. 13% (n=4) in each group had positive bronchial washings on admission, more in the control group had positive samples on broncho-alveolar lavage on day 3 (42% vs 7%; $P<0.01$); culture results beyond this did not differ. There were no significant differences in daily WBC, CRP, pro-calcitonin or CD 64 from day 1 to 5; CRP and procalcitonin were significantly higher in the control group on day 6 to 7 (all primary outcomes). Clinical outcomes did not vary between groups.

Should we give prophylactic antibiotics to patients with OHCA?

Not yet. There was no clinical effect from the excess in positive cultures at day 3. The study was limited by size, crossover, and use of 32 to 34 °C hypothermia. The target P-value for the primary outcomes should probably have been adjusted for multiple comparisons.



ADVANCED

Günther SC, Schwebel C, Hamidfar-Roy R, Bonadona A, Lugosi M, Ara-Somohano C, et al.. Complications of intravascular catheters in ICU: definitions, incidence and severity. A randomised controlled trial comparing usual transparent dressings versus new-generation dressings (the ADVANCED study). Intensive Care Med 2016;42(11):1753-1765

Catheter-related blood stream infections (CRBSIs) have become a key marker of care quality in ICUs, with evidence their incidence can be markedly reduced by consistently good clinical care.¹ Other post-insertion complications of central venous catheters (CVCs), peripheral venous catheters (PVCs) and arterial lines include thrombosis, phlebitis, local infection, catheter failure, extravasation and unplanned removal. This randomised controlled trial aimed to assess these complications alongside evaluating a new transparent dressing.

686 adult patients requiring any catheter and admitted to an 18-bed ICU in Grenoble, France over a year were recruited. 58 were excluded (45 catheter insertion failure, 13 protocol violations). 316 patients were randomised to the new dressing (3M™ IV Advanced, intervention group) and 312 to the control group (3M™ HP dressing, replaced during the study with Smith & Nephew's IV3000™). A chlorhexidine-impregnated sponge was placed under all dressings which were inspected once per shift. The intervention / control groups received 1142 / 1072 catheters and 2541 / 2295 dressings respectively.

Overall complication rates were high, but mostly minor. PVCs / arterial lines had complications in 28% / 30%, but severe in only 1%. CVCs had complications in 18% but 4% (20) were severe. There were complications in 31% of dialysis / pulmonary arterial catheters with 19% severe. Most severe complications were thrombotic, including 1 death. Significant CRBSI was rare, occurring in 2 patients (0.3/1000 catheter days). There was no difference in any complication rates between the different dressings (primary outcome).

Should we change our CVC dressings today?

No. However we should be aware that a low 'headline' CRBSI rate may obscure a significant rate of other catheter-related complications.

1. Pronovost P, Needham D, Berenholtz S, et al. An Intervention to Decrease Catheter-Related Bloodstream Infections in the ICU. N Engl J Med 2006;355(26):2725–32.



EPO-ACR-02

Cariou A, Deye N, Vivien B, Richard O, Pichon N, Bourg A et al. Early High-Dose Erythropoietin Therapy After Out-of-Hospital Cardiac Arrest – A multi-centre, Randomised Controlled Trial. J Am Coll Cardiol 2016; 68(1):40 – 49

EPO-ACR-02 was a single blinded, multi-centre randomised controlled trial investigating whether erythropoietin (EPO) administration to comatose survivors of out-of-hospital cardiac arrest would improve neurological outcome. Randomisation could occur either pre-hospital or at hospital admission, with the intervention, 40,000 units of EPO, administered i.v. as soon as possible after randomisation. This was followed up with a further 4 doses, each 12 hours apart, during the first 48 hours. The control group received standard post-resuscitation care without EPO.

The primary outcome was the percentage of patients achieving level 1 on the Cerebral Performance Category (CPC) scale at day 60 (survival with no or minimal neurological sequelae). All-cause mortality, adverse events and distribution on the CPC scale at different time points were secondary outcomes. A modified intention-to-treat analysis included 234 patients in the treatment groups and 242 in the control group. Groups were well matched at baseline. 99.1% (n=232) of patients received the first dose of EPO, with 75.6% (n=177) receiving all 5 doses.

There was no significant difference between the groups for the primary outcome, 32.4% vs 32.1% in the treatment and control groups, respectively, (95% CI, 0.68 to 1.48; P=0.96). The mortality rate was similar in both groups at all time points. The treatment group had a higher rate of adverse events (22.6% vs 14.9%; P=0.03), especially thrombosis (12.4% vs 5.8%; P=0.01).

Should we use erythropoietin in the management of post cardiac arrest patients?

No. EPO did not improve neurological outcome, but caused a higher rate of complications in this study.



GLIP1

Wiberg S, Hassager C, Schmidt H, Thomson JH, Frydland M, Lindholm MG et al. Neuroprotective Effects of the Glucagon-Like Peptide-1 Analogue Exenatide After Out-Of-Hospital Cardiac Arrest - A Randomised Controlled Trial. *Circulation* 2016;134:2115-24

Exenatide is a glucagon-like peptide-1 (GLIP-1) analogue shown to reduce glutamate-dependent cell death and oxidative stress in vitro, potentially providing protection against ischaemia-reperfusion injury. This Danish twin-centre, double-blind, randomised, placebo controlled trial was a safety and feasibility study of exenatide in survivors of out-of-hospital cardiac arrest (OHCA).

Patients with a witnessed OHCA of presumed cardiac origin, and who had sustained return of spontaneous circulation (ROSC) for > 20 minutes, and were not requiring mechanical circulatory support, were eligible for inclusion. Randomisation occurred after hospital admission. The intervention consisted of a single dose of 17.4 mcg of exenatide administered as an infusion over 6 hours 15 minutes, initiated as soon as possible after ROSC. Patients randomised to the control group received the infusion without active study drug over the same time period. All participants were blinded. Both groups received standard ICU care, including targeted temperature management at 36 °C.

The co-primary endpoints were (1) feasibility – defined as initiation of the intervention within 240 minutes of ROSC in > 90% of survivors and (2) efficacy – as indicated by the area under the curve for neurone specific enolase (NSE) from 24 to 72 hours. NSE is a biomarker which correlates with neuronal cell death.

90% (n=120) of screened patients were enrolled. No significant differences existed in baseline characteristics between groups. The modified intention-to-treat population consisted of 118 patients (treatment group, n=60; control group, n=58). Study drug was initiated in 58 intervention patients and 56 control patients, respectively, commencing within 240 minutes of ROSC in 96% of patients (n=110). The infusion of study drug was completed in 98%. No significant difference in the median area under the NSE curve was detected within the first 72 hours; exenatide vs placebo, 1307 (IQR 884 to 2093) µg×48 hours/L vs 1192 (888 to 1930) µg×48 hours/L; P=0.46. No differences in adverse events was detected between groups. The intervention group had a slightly lower median blood glucose level at 8 hours post admission (5.8 mmol/l vs 7.3 mmol/l; P<0.0001).

Should we use exenatide post cardiac arrest?

No. Future trials powered for clinical and functional outcomes are needed.



Statin AKI Cardiac Surgery Trial

Billings F, Hendricks P, Schildcrout S, Shi Y, Petrachek M, Byrne J et al. High Dose Perioperative Atorvastatin and Acute Kidney Injury Following Cardiac Surgery - A Randomised Clinical Trial. JAMA 2016; 315(9):877-888

This single-centre, randomised, double-blind, placebo-controlled trial tested whether a perioperative, short course of high dose atorvastatin would reduce the incidence of acute kidney injury (AKI) in patients undergoing cardiac surgery.

The intervention regime was determined by whether patients were statin naïve or not. Statin naïve patients were randomised to receive either 80 mg of atorvastatin the day prior to surgery, followed by 40 mg per day, including the day of surgery, until hospital discharge, or a matching placebo regime. Patients who were already prescribed a statin continued their normal medication but were randomised either to 80mg atorvastatin on the day of surgery and 40 mg on the 1st post-operative day followed thereafter by their usual dose or to a matching placebo regime.

The primary outcome was the diagnosis of AKI as stage 1 to 3, according to the AKIN criteria, within 48 hours of surgery. Among secondary outcomes were the maximum increase in creatinine concentration within 48 hours of surgery, incidence of delirium and atrial fibrillation.

653 patients were randomised, with 615 included in the primary analysis (treatment group n=308 vs control group n=307). Recruitment of statin naïve patients was discontinued after the second interim analysis due to a signal of harm, especially in those with chronic kidney disease. The trial was subsequently also terminated for patients already on a statin due to perceived futility for the primary outcome based on data for patients who had completed the study.

Baseline characteristics were well balanced between groups. 98.2% of all study drug protocol-directed doses were given. In those who were statin naïve, AKI occurred in 21.6% of the treatment group vs 13.4% of the control group (RR 1.61; 95% CI, 0.78 to 1.46; P=0.15). In those already taking a statin, high dose treatment or short course withdrawal did not affect incidence of AKI, 20.4% vs 22.4%, respectively (RR 0.91; 95% CI, 0.63 to 1.32; P=0.63). The adverse event rate did not differ between groups.

Should we implement this into our practice?

No. There is no evidence to suggest perioperative initiation of high dose statins reduces the risk of AKI in cardiac surgical patients. In statin naïve patients this approach may be harmful.



The Best of the Rest: RESPIRATORY

OPTINIV

Jaber. Apnoeic oxygenation via high-flow nasal cannula oxygen combined with non-invasive ventilation preoxygenation for intubation in hypoxaemic patients in the intensive care unit: the single-centre, blinded, randomised controlled OPTINIV trial. Intensive Care Med 2016;42(12):1877-1887

High-flow nasal oxygen (HFNO) has an evolving role in the critically ill. A recent review identified 22 trials enrolling over 2800 patients published over the past 5 years, many with positive results.¹ Both HFNO and non-invasive ventilation (NIV) have been used to pre-oxygenate before emergent tracheal intubation in acute hypoxaemic respiratory failure (AHRF), potentially offering apnoeic oxygenation (HFNO) or alveolar recruitment (NIV ± HFNO), but they have not previously been studied in combination.

This randomised controlled trial was conducted in Montpellier, France. 50 consecutive ICU patients requiring intubation for AHRF were enrolled with consent (self, surrogate ± deferred). Baseline characteristics were similar, median age was 61, 78% were male, median PaO₂:FiO₂ was 122 mm Hg, 94% were characterised as an emergency. The control group received 4 mins pre-oxygenation with NIV (Pressure Support / PEEP 10/5 cmH₂O) with high flow nasal cannulae in situ but not on; the intervention group received this alongside active HFNO (60 l/min, FiO₂ 100%). The data-collecting observer (but not the operator) was blinded by a sheet placed over the HFNO flow meter and a further high flow nasal oxygen cannula running under the sheet to mimic sound. One patient was excluded from analysis (failed SpO₂ trace).

The minimal median SpO₂ during intubation was significantly higher in the intervention group (primary outcome, SpO₂ 100% vs 96%, P=0.029). Time to intubation and oxygenation before or beyond intubation did not vary. Severe desaturation (SpO₂ <80%) occurred in one intervention and five control patients (P=0.098). Overall complication rates and patient outcomes did not vary.

Should we use HFNC for all ICU intubations?

Not yet – A randomised controlled trial powered for patient outcomes is required. In the meantime it could be considered, especially if already in-situ.

1. Papazian L, Corley A, Hess D, Fraser JF, Frat JP, Guitton (2016) Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review. Intensive Care Med 42:1336–1349



TRACHUS

Gobatto . Ultrasound-guided percutaneous dilational tracheostomy versus bronchoscopy-guided percutaneous dilational tracheostomy in critically ill patients (TRACHUS): a randomised noninferiority controlled trial. Intensive Care Med 2016;42(3):342-351

Percutaneous dilational tracheostomy (PDT) within the ICU has a safety record comparable to an open surgical technique. Realtime fiberoptic bronchoscopic guidance (FOB) during the procedure is commonly felt to offer safety advantages. Several reports document the utility of pre-procedure ultrasound (US) scanning of the anterior neck to identify structures such as a large thyroid or superficial blood vessels which may prompt an open surgical approach. The use of US to replace FOB has been less well studied, with a 74-patient trial finding a higher number of mostly minor complications with bronchoscopic guidance (including a 22% incidence of tracheal cuff puncture)¹. TRACHUS aimed to establish the non-inferiority of US guidance.

123 Brazilian patients were randomised (two in error). Three didn't have a PDT. US guidance included anatomy scanning, selection of puncture site, withdrawal of endotracheal tube cuff to cricoid level, realtime tracheal puncture and confirmation of guide wire placement. Bronchoscopy was available but defined the attempt as a failure. In the FOB group the scope was used to visualise ETT withdrawal, tracheal puncture and dilatation. Griggs dilating forceps were used in all cases. Ultrasound changed the puncture site in 23% of patients. The procedure length and operator-described difficulty was similar in both groups. Procedure failure (primary outcome) due to the major complication of tracheal laceration occurred in 1 patient in each group (zero difference, 90% CI, -5.5 to 5.85; met pre-specified criteria for non-inferiority). Minor complications occurred in 33% / 21% of the US / FOB groups (non-significant). Clinical outcomes were similar.

Should we abandon the fibroscope in Percutaneous Tracheostomies?

No – The techniques seem complimentary, with combining US to examine the front-of-neck and guide puncture and FOB to confirm placement and observe the back wall of the trachea, and assist with complications. Caution should be applied to applying this trial to non-Griggs techniques such as single-dilator.

1. Ravi PR, Vijay MN (2015) Real time ultrasound-guided percutaneous tracheostomy: is it a better option than bronchoscopic guided percutaneous tracheostomy? Med J Armed Forces India 71:158–164



Steroids in ARDS

Tongyoo S, Permpikul C, Mongkolpun W, Vattanavanit V, Udompanturak S, Kocak M, et al. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomised controlled trial. *Critical Care* 2016;20:329

Tongyoo and colleagues completed a single-centre, blinded, parallel-group, randomised controlled trial evaluating the efficacy of hydrocortisone therapy in early sepsis-associated ARDS. Eligible patients were aged over 18 years of age, had severe sepsis or septic shock, and developed ARDS within 12 hours of the onset of mechanical ventilation. Randomisation was in a 1:1 fashion. Patients received either IV hydrocortisone 50 mg every 6 h for 7 days or placebo. Sepsis management was consistent with the Surviving Sepsis Campaign guidelines and protective mechanical ventilation was used. 194 patients were required to identify an absolute mortality reduction of 20%, from an expected control mortality of 60% at 28 days, with 80% power and at a 2-sided 5% significance level.

634 adults with severe sepsis or septic shock were screened and 206 recruited and randomised. Nine withdrew consent and were excluded from analysis. Groups were similar at baseline, with 98 allocated to the hydrocortisone group and 99 to the control group. 154 patients had septic shock and 135 moderate-to-severe ARDS. Pneumonia was the most common cause of sepsis. The achieved delivery of hydrocortisone, and the separation of groups in terms of the trial intervention, was not stated.

There was no difference in the primary outcome of mean mortality at 28 days; hydrocortisone group 22% (SD 22.5) vs control 27% (SD 27.3); RR, 0.82; 95% CI, 0.50 to 1.34; P=0.51. Similarly, there was no difference in the secondary outcomes of 60-day mortality (34.7% vs 40.4%) or any organ-support measures, such as duration of mechanical ventilation (11.8 vs 13.9 days), duration of vasopressor support (4.8 vs 6.8 days) or requirement for renal replacement therapy (22% vs 22%). Hydrocortisone administration was associated with higher rates of hyperglycaemia.

Should we routinely used steroids in sepsis-associated ARDS ?

No, the evidence remains weak for the routine use of steroids in ARDS, including in the setting of sepsis.



IASIS

Kollef MH, Ricard, JD, Roux D, Francois B, Ischaki E, Rozgonyi, et al. A randomised trial of the amikacin fosfomycin inhalation system for the adjunctive therapy of Gram-negative ventilator-associated pneumonia: IASIS Trial. Chest 2016;published November 24th

IASIS was a randomised double-blind, placebo-controlled, parallel group, phase 2 trial conducted across Europe and the United States investigating the effect of nebulised amikacin with fosfomycin in Gram-negative ventilator-associated pneumonia. Adult patients were eligible if they were ventilated with a diagnosis of pneumonia, defined as new or progressive chest radiograph infiltrates with signs of infection (fever $>38^{\circ}\text{C}$, WCC $<4,000/\text{mm}^3$, or $\geq 12,000/\text{mm}^3$), plus hypoxia ($\text{PaO}_2/\text{FiO}_2 \leq 350$ mm Hg) and an APACHE II score >10 in the previous 24 hours, and in the presence of a Gram-negative organism in respiratory secretions within the previous week. Patients were randomised to AFIS (amikacin fosfomycin inhalation system containing 300 mg amikacin and 120 mg fosfomycin) or placebo administered twice daily while ventilated for up to 10 days. In addition, all patients received IV meropenem or imipenem for a minimum of 7 days.

The primary endpoint was the change from baseline in clinical pulmonary infection score (CPIS) during the intervention period. A sample size of 140 patients provided 80% power at a 2-sided 5% significance level, to detect an effect size (difference in means/standard deviation) of 0.53 at any given timepoint in the CPIS.

143 patients were randomised to AFIS ($n=71$) or placebo ($n=72$). Patients were similar at baseline. Gram-negative bacteria were present in 142 patients. All patients received at least one dose of AFIS/placebo, with 65 patients receiving all 10 days therapy. Treatment was discontinued in just 3 patients due to adverse effects.

CPIS improvement from baseline did not differ between groups ($P = 0.70$). Mean (\pm SD) CPIS at day 10 were 5.0 ± 3.1 for the AFIS group compared with 4.8 ± 3.4 in the placebo group ($P = 0.81$). There was no difference in the secondary endpoint of no mortality and clinical cure at day 14 or earlier ($P=0.68$) nor in the endpoint of no mortality and ventilator-free days ($P=0.06$). 24% of the AFIS died, compared with 17% of the placebo group; $P=0.32$. The AFIS group had significantly fewer positive tracheal cultures on days 3 and 7, although the placebo group had more ventilator-free days up to 28 days (12.5 (9.72) vs 9.8 (9.7); $P=0.02$).

Should we routinely use amikacin fosfomycin inhalation system for the adjunctive therapy of Gram-negative ventilator-associated pneumonia?

No. In patients with gram negative pneumonia, despite reducing positive tracheal cultures, nebulised amikacin with fosfomycin had no effect on clinic outcomes.



Probiotics for the Prevention of VAP

Zeng J, Wang CT, Zhang FS, Qi F, Wang SF, Ma S, et al. Effect of probiotics on the incidence of ventilator-associated pneumonia in critically ill patients: a randomised controlled multi-centre trial. *Intensive Care Med* 2016;42(6):1018-1028

Zeng and colleagues undertook a Chinese open-label, multi-centre, parallel group, randomised controlled trial evaluating the effect of probiotics on the development of ventilator-associated pneumonia in critically ill patients. Eligible patients were adults expected to be mechanically ventilated for at least 48 hours. Major exclusion criteria were age over 80 years, an APACHE II score ≥ 25 , a preceding duration of mechanical ventilation > 72 hours, a failure of enteral nutrition and immunosuppressive therapy. Patients were enrolled within 24 hours of initiation of invasive mechanical ventilation.

The intervention consisted of probiotic capsules, containing live *Bacillus subtilis* and *Enterococcus faecalis* (Medilac-S) 0.5 g three times daily through a nasogastric feeding tube for up to 14 days. Both groups also received standard preventive strategies against the development of VAP, including daily screening for extubation potential, hand hygiene, aspiration precautions and prevention of contamination. Patients were positioned in the semi-recumbent position, intubated with tracheal tubes capable of subglottic suctioning, and had their tracheal tube cuff pressures maintained at approximately 25 cmH₂O. 234 patients were required to detect a decrease in the incidence of VAP by 20%, from 60% to 40%, with 80% power at the 5% significance level, allowing for a 10% dropout rate. Patients were screened daily for the development of VAP, which was diagnosed clinically on the presence of two out of three of: new chest radiograph infiltrates, hyper- or hypo-thermia, and a high or low white cell count.

457 patients were screened and 250 randomised, with most excluded patients having a predicted duration of mechanical ventilation < 48 hours. Groups were similar at baseline. The study drug was administered on 95.8% of study days. Although the probiotic group had a non-statistically significant lower incidence of clinically determined VAP (40.7% vs 53.0%; $P=0.059$), the incidence of microbiologically confirmed VAP was significantly reduced (36.4% vs 50.4%; $P=0.031$). There was no between group difference in identified pathogens. Probiotics results in a longer time to development of VAP (10.4 days vs 7.5 days; $P=0.022$). There were no differences in clinical outcomes, There was a non-significant increase in ICU mortality with probiotics (12.7% vs 7.7%; $P=0.207$), which was lost at the end-point of hospital mortality (10.7% vs 14.8%).

Should we routinely use probiotics to prevent ventilator-associated pneumonia?

No, there is no robust evidence suggesting benefit from this intervention in VAP.



EVDCPR

Kim JW, Park SO, Lee KR, Hong DY, Baek KJ, Hwan Y, et al. Video laryngoscopy vs direct laryngoscopy: which should be chosen for endotracheal intubation during cardiopulmonary resuscitation?: A prospective randomised controlled study of experienced intubators. Resuscitation 2016;105:196-202

Endotracheal intubation (ETI) during cardiac arrest is a high-risk event with potential difficulties both in tracheal tube insertion and recognition of failure. Reasons include ongoing CPR, seniority of operator, patient positioning, cervical collars, airway soiling and capnography being unavailable or difficult to interpret. There is also concern about the effect of interruptions to chest compressions, leading expert bodies to recommend novices use supraglottic airways as a first line. Video-laryngoscopes (VL) have the potential to improve outcomes, but experienced intubators may prefer a traditional direct laryngoscope (DL).

Emergency Physicians were randomised to use VL (Glidescope®) or DL to intubate patients arriving in their (Korean) Emergency Department in cardiac arrest, and scheduled to be on duty on different shifts. 270 sequential patients were intubated, 130 were excluded (120 as the operator was inexperienced (<50 prior intubations)). Resuscitations were recorded on CCTV and compressions captured by the monitor / defibrillator. 69 ETIs by DL and 71 by VL were analysed, there was no difference in successful ETI (primary outcome, DL 93% vs VL 96%; P=0.49). Time to complete ETI also did not vary (median 51 vs 42 s; P=0.143).

There was a longer duration of interruptions to compressions with DL vs VL (median 4 vs 0 seconds, P<0.001) and more “serious” (>10 s) interruptions (26% of cases vs 0%, P<0.001). There were 3 oesophageal intubations and 5 dental injuries in the DL group and 1 dental injury in the VL group (NS), most with operators with <100 previous intubations.

Should we abandon the Macintosh laryngoscope in cardiac arrest?

Not necessarily. Intubation rates were equivalent but video scopes have the potential advantages of less interruption to CPR and bystander verification of tracheal intubation. Novices may wish to train with a VL if available. Complication rates with DL may merit further study.



NAVA vs Pressure Support

Demoule A, Clavel M, Rolland-Debord C, Perbet S, Terzi N, Kouatchet A et al. Neurally adjusted ventilator assist as an alternative to pressure support ventilation in adults: a French multi-centre randomised trial. *Intensive Care Med* 2016;42:1723

Demoule and colleagues undertook a multi-centre RCT evaluating whether during the first 48 hours of transition from controlled mandatory ventilation to partial ventilator support, neurally adjusted ventilation (NAVA) would allow patients to remain in a partial ventilator support mode for a longer duration than pressure support ventilation (PSV).

Patients with acute respiratory failure from a primary respiratory cause, who had been ventilated for > 24 hours and expected to remain so for > 48 hours were eligible for inclusion. A number of other pre-defined inclusion criteria were required to be met. The primary outcome measure was the likelihood of patients remaining in a partial ventilator support mode without a return to controlled mandatory ventilation in the first 48 hours. Patient-ventilator asynchrony and duration of mechanical ventilation were among the secondary outcomes.

128 patients were enrolled, 62 in the NAVA group and 66 in the PSV group. The NAVA group had more men (76% vs 59%) and the PSV group had a higher Charlson co-morbidity score. Groups were otherwise well matched.

The NAVA group spent 44.1 hours (33.0 to 47.8) in NAVA mode vs 47.1 hours (39.8 to 48.0) in the PSV mode for those randomised to the PSV group ($P=0.55$). No significant difference in the primary outcome, the proportion of patients remaining in partial ventilatory mode, was seen (67.2% vs 63.3%, respectively; $P=0.66$). The NAVA group had less patient-ventilator asynchrony (asynchrony index, 14.7% vs 26.7%; $P=0.001$), more ventilator free-days at day 7 (1 vs 0) but not day 28 (21 vs 17; $P=0.12$). NAVA resulted in less need for post-extubation NIV (43.5% vs 66.6%; $P=0.01$). There was no difference in 28 day mortality (15.0 vs 22.7 %, respectively; $P=0.21$)

Should we implement this into our practice?

No. We should await the results of larger trials looking at more relevant patient-centred outcomes before adopting NAVA as the principle partial ventilatory support modality.



The Best of the Rest: HEPATOBILARY

Terlipressin vs Noradrenaline in Cirrhotic Septic Shock

Choudhury A, Kedarisetty CK, Vashishtha C, Saini D, Kumar S, Maiwall R, et al. A randomised trial comparing terlipressin and noradrenaline in patients with cirrhosis and septic shock. Liver Int 2016;epublished September 16th

Terlipressin, a synthetic vasopressin analogue, has an established role in hepatorenal syndrome and variceal bleeds. Septic shock in decompensated cirrhosis carries a mortality of up to 70%. The effectiveness of terlipressin in this setting is unclear.

Patients admitted to a liver ICU in New Dehli over 18 months with known cirrhosis and septic shock (presumed infection, 2 SIRS criteria, need for vasopressor to maintain MAP ≥ 65 mm Hg after 15 ml/kg saline and 100mls 5% albumin) were screened. 427 of 511 patients were excluded, mostly for history of cardiovascular disease or previous adverse reaction to terlipressin. 84 were randomised to an infusion of terlipressin (1.3 to 5.2 $\mu\text{g}/\text{min}$, totalling 2 to 8 mg/24 hours) or noradrenaline (7.5 to 60 $\mu\text{g}/\text{min}$) titrated to a MAP ≥ 65 mm Hg. Rescue therapy was a combination of the two drugs. Septic focus was imbalanced between the terlipressin / noradrenaline groups: spontaneous bacterial peritonitis was present in 50% / 26% and pneumonia in 21% / 48%. The primary outcome was the ability to maintain MAP > 65 mm Hg for the initial 48 hours.

There was significant crossover between groups. At 48 hours the success of monotherapy in the terlipressin and noradrenaline groups was 48% and 36%, respectively. Salvage therapy was required in 24% and 33%, with drug discontinued for side effects in 24% and 2%, predominantly due to peripheral cyanosis with terlipressin. In the intention-to-treat analysis, the primary outcome favoured terlipressin (93% vs 69%; $P=0.05$), but this was severely compromised by the crossovers. Overall survival at 28 days was 20%; with no difference between groups. Early survival favoured the terlipressin group, as did non-significant trends in tissue perfusion parameters (lactate clearance, decrease in ScvO₂). The group able to be maintained on terlipressin alone had a better outcome.

Should we implement this into our practice?

No. This study was too limited by a failure of treatment separation and imbalance in source of sepsis. Terlipressin remains, however, a useful adjunct in these patients.



The Best of the Rest: RENAL

SALT

Semler MW, Wanderer JP, Ehrenfeld JM, Strollings JL, Self WH, Slew ED, et al. Balanced Crystalloids versus Saline in the Intensive Care Unit: The SALT randomised Trial. Am J Respir Crit Care Med 2015; published October 17th

The SALT (isotonic Solution Administration Logistical Testing) trial was an American single-centre, pilot, open-label, cluster-randomised, multiple-crossover trial. 947 adults received either 0.9% sodium chloride or a balanced crystalloid (Lactated Ringers or Plasmalyte A), with the administered fluid alternating on a monthly basis. The fluid to be administered for the first month was randomly chosen.

As the study had a waiver of informed consent, all patients admitted to this ICU were automatically enrolled in the study. The amount, rate and indications for fluid administration was at the discretion of the treating physician. The alternative fluid could be administered if the treating clinician determined a clinical need existed. The presence of head injury or hyperkalaemia were relative contraindications for the receipt of a balanced crystalloid. Wash-in and-out periods were not used, so patients traversing adjacent months could be exposed to more than one study fluid. 1,000 patients were required to test the primary outcome of a 60% absolute difference in the type of fluid administered (saline vs balanced crystalloid).

All patients admitted to the ICU during the study period (February to May 2015) were enrolled in the study. Groups were similar at baseline. During the months where a balanced crystalloid was the chosen fluid, 92.2% of fluid orders were for a balanced crystalloid. This was similar in the months assigned to saline, with 95.2% of orders being for this fluid. Total volumes of administered fluid appeared similar in the two groups. The highest serum chloride in the study period was minimally higher in the saline group (median 109 mmol/L vs 108 mmol/L; $P=0.03$). Potassium may have been slightly higher in the balanced crystalloid group, although the absolute value wasn't stated. There was no difference in creatinine levels, either the highest value, the change from baseline or final creatinine. The incidence of stage II kidney injury or higher did not differ either. There was a signal towards higher serum chloride and creatinine levels, more kidney injury and a greater requirement for renal replacement therapy, in the subgroup assigned to saline and who received a large volume of fluid.

Should we desist from routinely using 0.9% saline in critically ill patients ?

No. This pilot trial sought to determine the feasibility of achieving separation in the delivery of saline versus balanced crystalloids.



The Best of the Rest: METABOLIC

Thiamine in Septic Shock

Donnino M, Andersen L, Chase M, Berg K, Tidswell M, Giberson T et al. Randomised, Double-Blind, Placebo-Controlled Trial of Thiamine as a Metabolic Resuscitator in Septic Shock: A Pilot Study. Crit Care Med 2016;44(2):360-367

As sepsis results in a failure of many key metabolic pathways, and thiamine has a central role in mitochondrial metabolism, Donnino and colleagues completed a pilot two-centre randomised controlled trial, evaluating the metabolic effects of thiamine administration in patients with septic shock. Those eligible for inclusion had septic shock (SIRS due to suspected infection and hypotension despite ≥ 2 L of i.v. fluid followed by infusion of vasopressor) and hyperlactaemia (> 3 mmol/L). Patients already receiving thiamine or with liver dysfunction were excluded. The intervention group received 200 mg thiamine i.v. twice daily for 7 days or until hospital discharge. The control group received placebo. All participants in the study were blinded.

The primary outcome measure was the lactate level 24 hours after the first dose was administered. Secondary outcome measures included lactate levels at 6, 12 and 24 hours, APACHE II and SOFA scores at 24 hours and length of stay as well as in-hospital mortality.

Eighty patients were required to identify a 67% relative reduction in lactate levels at 24 hours, with a further 10% recruited to allow for attrition. Ninety-two patients were randomised, 45 to thiamine and 47 to placebo, with 2 patients in each group not receiving the study drug. Groups were well matched at baseline, although the thiamine group had a higher proportion of non-insulin dependent diabetes mellitus (32% vs 2%).

There was no significant difference in the primary outcome of absolute change in lactate levels at 24 hours. Like the other secondary outcomes, in-hospital mortality was similar between groups, 42% vs 44%, $P=0.86$. Subgroup analysis showed 35% ($n=28$) of patients were thiamine deficient at baseline; those in the intervention group had significantly lower lactate levels at 24 hours, median 2.1 mmol/L (IQR, 1.4 to 2.5) vs 3.1 mmol/L (1.9 – to 8.3); $P=0.03$.

Should we implement this into our practice?

No. Larger trials are required to clarify any role thiamine may have in septic shock.



The Best of the Rest: HAEMATOLOGY

INFORM

Heddle NM, Cook RJ, Arnold DM, Liu Y, Barty R, Crowther MA, et al. Effect of Short-Term vs Long-Term Blood Storage on Mortality after Transfusion. N Engl J Med 2016;375:1937-1945

This multi-centre, international, open-label, randomised, controlled trial investigated the effect of duration of storage of blood prior to transfusion in a general hospitalised population. Patients aged ≥ 18 who required red blood cell (RBC) transfusion were eligible. In this pragmatic trial, the decision to transfuse was at the discretion of the treating clinician. Patients were randomly allocated in a 1:2 ratio to receive either the freshest RBC available (short-term storage group) or the oldest (long-term storage group). Randomisation was stratified based on study centre and blood type.

The primary outcome measure was in-hospital mortality. The investigators sought to achieve a minimum difference of 10 days storage duration between the two groups. As this would be difficult to achieve for blood groups B and AB, the primary analysis was based on blood groups A and O only. Assuming a 10% mortality in the long-term storage group, 24,400 patients of any blood type would be required to provide a power of 90% to detect a 15% relative risk reduction with the transfusion of short-term storage RBC. After an interim analysis the target sample size was increased to 31,497 patients.

Over a 3 year period, 31,497 patients were randomised, 6761 patients were excluded after randomisation (5879 as no RBC were transfused). Ultimately, 20,858 patients with blood group A and O were included in the primary analysis; 6936 were randomised to the short-term and 13,922 to the long-term storage group. Groups were well balanced.

A total of 76,356 RBC were transfused. The mean storage duration was 13.0 ± 7.6 days vs 23.6 ± 8.9 days in the short-term and long-term storage groups respectively ($P < 0.001$). There was no difference in the primary outcome measure of in-hospital mortality in patients with blood group A or O; 9.1% in the short-term vs 8.7% in the long-term storage groups (OR, 1.05; 95% CI, 0.95 to 1.16; $P = 0.34$). Pre-specified subgroup analysis in patients in ICU, those who had undergone cardiovascular surgery, and patients with cancer demonstrated no mortality difference between the two groups.

Should we transfuse the freshest blood available?

No. This is further evidence that using fresher blood confers little benefit.



The Best of the Rest: SEPSIS

Dopamine vs Adrenaline in Paediatric Septic Shock

Ramaswamy. Double-Blind randomised Clinical Trial Comparing Dopamine and Epinephrine in Pediatric Fluid-Refractory Hypotensive Septic Shock. *Pediatr Crit Care Med* 2016;17(11):e502-e512

Ramaswamy and colleagues completed a single-centre, pilot, parallel group, randomised trial in India, comparing dopamine with adrenaline in paediatric septic shock. Eligible children were aged between 3 months and 12 years, had fluid-refractory hypotensive cold septic shock, and were in the ICU. Exclusion criteria included preexisting heart disease or arrhythmia, current vasoactive support, raised intra-cranial pressure, known immune compromised state, and severe acute malnutrition. Randomisation was performed with the use of sealed envelopes, with group allocation occurring in variable blocks. Both groups received the study group and a placebo, with dopamine infused at 10 to 20 µg/kg/min and adrenaline infused at 0.1 to 0.3 µg/kg/min. Open-label adrenaline was added if maximum infusion rates were met. Sepsis management was according to the Surviving Sepsis Guidelines. As this was a pilot trial, a convenience sample of 60 children was enrolled. The primary outcome was resolution of shock within first hour of resuscitation, defined by warm extremities, a urinary output > 1 ml/kg/hr, capillary refill < 3 seconds, normal mental status, plus a normal heart rate and blood pressure above the 5th percentile for age. Analysis was by intention-to-treat.

210 patients were screened, 61 were eligible and 60 were randomised, 29 to adrenaline and 31 to dopamine. Groups had similar clinical and demographic characteristics at baseline, with 27 children requiring invasive mechanical ventilation. Full follow-up was achieved. A greater proportion of patients in the adrenaline group achieved resolution of shock in the first hour (41.4% vs 12.9%; RR, 3.2; 95% CI, 1.16 to 8.82 P=0.019; OR, 4.8%; 95% CI, 1.3 to 17.2; absolute risk reduction 28.5%, number needed to treat of 3). Fluid therapy, vasoactive support and red cell transfusion was similar between groups up to 6 hours post randomisation. There was no difference in the proportion of children with resolution of shock at 6 hours (adrenaline, 48.3% vs dopamine, 29%; OR, 2.01; 95% CI, 0.7 to 5.7; P=0.18). 28 day mortality was also similar (adrenaline, 48.3% vs dopamine, 58.1%, RR, 0.83; 95% CI, 0.51 to 1.34; P=0.605). The mean duration of mechanical ventilation was significantly shorter in the adrenaline group, 9(65.5) vs 28(90.3) days; RR 0.72; 95% CI, 0.54 to 0.97; P=0.028. Adverse event rate was similar.

Should we routinely use dopamine in the management of paediatric septic shock ?

No. This trial joins the growing adult evidence base suggesting harm with dopamine in sepsis.



The Best of the Rest: MISCELLANEOUS

ICU Family Communication Study

Curtis JR, Treece PD, Nielsen EL, Gold J, Ciechanowski PS, Shannon SE, et al. randomised Trial of Communication Facilitators to Reduce Family Distress and Intensity of End-of-Life Care. Am J Respir Crit Care Med 2016;193(2):154-162

Support of patients' families is an integral part of ICU end-of-life care. Evidence from the authors' group, and others, suggests multidisciplinary interventions can improve patient care and family outcomes, such as post-traumatic stress disorder (PTSD) or depression. This trial studied the introduction of a separate nurse or social worker trained to be a 'facilitator' interfacing between families and clinicians.

Families of ICU patients with a predicted mortality $\geq 30\%$ were recruited from 5 Seattle (USA) ICUs (both 'open' and 'closed'). In the intervention group, the facilitators managed communication, supported the families and offered follow-up; families randomised to the control group received usual care. 268 family members from 170 patients were enrolled, 131 to intervention and 137 to control. Groups were well matched but 42% / 55% were lost to 6-month follow up in the intervention / control groups.

Depression, PTSD and anxiety were assessed at 3 and 6 months. Only the 6-month depression scores were significantly affected, being lower in the intervention group when measured by the PHQ-9 questionnaire (2.4 vs 4.7; $P=0.017$). Mortality or frequency of withdrawal of life-sustaining treatment (WLST) did not vary, but time to WLST was longer in the control group (16.5 d vs 7.2 d; $P=0.001$), as was ICU length of stay in those who died (29 vs 8 days, $P=0.001$). Patient ICU costs were also higher in the control group (mean \$75,850 vs \$51,000 dollars, $P=0.042$).

Should we employ a nurse facilitator in our ICUs?

No. It is difficult to extrapolate these findings beyond this setting, particularly as it included open ICUs which are a completely different model of care. There seemed to be little impact on family psychological outcomes. The main effect seemed to be earlier end-of-life care. Further qualitative research may shed light on this aspect.



RAPIT

Jensen JF, Egerod I, Bestle MH, Christensen DF, Elklit A, Hansen RL, et al. A recovery program to improve quality of life, sense of coherence and psychological health in ICU survivors: a multi-centre randomised controlled trial, the RAPIT study. *Intensive Care Med* 2016;42(11):1733-1743

There has been significant progress made in defining the physical, psychological and cognitive sequelae of critical illness, but efforts to improve these with post-ICU recovery programs or follow-up clinics have generally had disappointing results when studied. Danish patients usually receive post-discharge physiotherapy, but there was no systematic availability of ICU-specific psychological support. The RAPIT trial was a pragmatic unblinded multi-centre randomised controlled trial conducted in 10 Danish ICUs, assessing the effectiveness of a nurse-led individualised psychological health program on patient outcomes.

2,105 adults who had been ventilated for >48 hours were screened within ICU. 386 consenting survivors without cognitive impairment were randomised at ICU discharge to the intervention or usual care. The intervention consisted of 3 specialist nurse-led consultations over 10 months and utilised a range of psychological techniques including cognitive behavioural therapy and the construction of illness narratives using photographs taken during the patient's ICU admission. The latter 2 consultations were by telephone and directed by prompt sheets completed beforehand. Standard care included the same physical rehabilitation but no ICU follow up.

After excluding those who died or were lost to follow up, data was available on 116 intervention and 119 control patients. There were no statistically significant differences between the groups at 3 or 12 months in physical or mental health-related quality of life scores (HRQOL, primary outcome); or scores for depression, anxiety or post traumatic stress disorder (secondary outcomes). In all, 48 separate statistical analyses were presented on these outcomes. Only one was significant (less anxiety at 3 months on per-protocol analysis). In general, scores were better than expected, perhaps relating to population characteristics or the physical rehabilitation received.

Should we be introducing this programme to our patients?

No. The search for reliable methods to impact on post-ICU morbidity continues.



Fragility Index

Ridgeon E, Young P, Bellomo R, Mucchetti M, Rosalba L, Giovanni L. The Fragility Index in multi-centre randomised Controlled Critical Care Trials. Critical Care Med 2016;44(7):1278-1284

Whether a trial intervention is successful or not has traditionally been defined by the finding of a statistically significant difference between groups for a binary outcome such as mortality; usually stated as a P value (the probability of finding the observed, or more extreme, results if the null hypothesis is true) of less than 5% ($P < 0.05$). Many published trials reach this threshold but are subsequently not replicable or even reversed. For successful mortality trials, the fragility index states how many extra patients would have had to die in the control group for the P value to breach the $P=0.05$ threshold; a low number suggests the trial result is not robust. Online calculators are available, e.g. <http://clincalc.com/Stats/FragilityIndex.aspx>

The authors identified 862 multi-centre critical care trials and analysed 56 which investigated nonsurgical interventions in critically ill adults and reported a specific time-point mortality with $P \leq 0.05$. The fragility index was calculated using two-by-two contingency tables and iteratively adding to the group with the smallest number of deaths until $P \geq 0.05$ by Fisher's exact test. They also assessed trial quality and effect size by the number needed to treat or harm (NNT/ NNH).

The median fragility index for all trials was 2 (IQR, 1 to 3.5, range 0 to 48). 42% of studies had a fragility index of 0 or 1; i.e, significance would be lost if one extra patient had died (zero could occur if significance was lost simply by changing from the chi-square to Fisher exact test). In seven studies the fragility index was less than the number lost to follow-up. 25% of studies had a fragility index of ≥ 3 . CRASH-2 had the highest. A higher fragility index tended to occur in larger trials ($n > 126$) reporting a lower P-value ($P \leq 0.02$). The authors conclude that critical care trials often have too small sample sizes and target unrealistic treatment effect sizes. This was described elegantly in this paper even with single-centre studies excluded. Logically a low fragility index should help to identify those studies which clinicians may wish to see replicated before changing practice.

Should we implement this into our practice?

Yes. Fragility indexes should be reported routinely in published critical care research.



Section 3



The Best Non-Paywalled Guidelines of 2016

Please note, some guidelines are available from the relevant society rather than directly from the publisher. For readers of the electronic pdf version of this book, the inbuilt hyperlinks connect to the accessible paper.

The Best Guidelines: **AIRWAY**

- Rehn. Scandinavian SSAI clinical practice guideline on pre-hospital airway management. *Acta Anaesthesiologica Scandinavica* 2016;epublished June 3rd
- Piepho. S1 guidelines on airway management. Guideline of the German Society of Anesthesiology and Intensive Care Medicine. *Der Anaesthesist* 2015;64(Supplement 1):27–40
- Myatra. All India Difficult Airway Association 2016 guidelines for the management of unanticipated difficult tracheal intubation in adults. *Indian J Anaesth* 2016;60:885-98
- Pawar. All India Difficult Airway Association 2016 guidelines for the management of unanticipated difficult tracheal intubation in Paediatrics. *Indian J Anaesth* 2016;60:906-14
- Kundra. All India Difficult Airway Association 2016 guidelines for the management of anticipated difficult extubation. *Indian J Anaesth* 2016;60:915-21
- Myatra. The All India Difficult Airway Association 2016 guidelines for tracheal intubation in the Intensive Care Unit. *Indian J Anaesth* 2016;60:922-30

The Best Guidelines: **NEURO**

- Trinka. A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015;56:1515–1523
- South African Acute Pain Guidelines 2016. Official publication of The South African Society of Anaesthesiologists (SASA)
- Fried. The Insertion and Management of External Ventricular Drains: An Evidence-Based Consensus Statement. A Statement for Healthcare Professionals from the Neurocritical Care Society. *Neurocrit Care* 2016;24:61–8
- Neurocritical Care Committee of the Chinese Society of Neurology (NCC/CSN). The Chinese Expert Consensus on Evaluation of Coma after Cardiopulmonary Resuscitation. *Chin Med J* 2016;129:2123-7
- Guidelines for the Management of Severe Traumatic Brain Injury 4th Edition
- Carney. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition *Neurosurgery* 2016;epublished September 22nd (*Executive Summary*)
- Frontera. Guideline for Reversal of Antithrombotics in intra-cranial Hemorrhage. A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care* 2016;24:6–46
- Murray. Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient. *Crit Care Med* 2016;44(11):2079-2103



The Best Guidelines: CIRCULATORY

- Canadian Guidelines for the use of targeted temperature management (therapeutic hypothermia) after cardiac arrest: A joint statement from The Canadian Critical Care Society (CCCS), Canadian Neurocritical Care Society (CNCCS), and the Canadian Critical Care Trials Group (CCCTG). *Resuscitation* 2016;98:48-63
- Harjola. Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. *Eur J Heart Fail* 2016;18(3):226-241
- Intravascular volume therapy in adults: Guidelines from the Association of the Scientific Medical Societies in Germany. *Eur J Anaesthesiol* 2016;33(7):488-521
- 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Journal of Heart Failure* 2016;18(8):891-975
- 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2016;epublished May 20th
- Nieminen. The role of levosimendan in acute heart failure complicating acute coronary syndrome: A review and expert consensus opinion. *International Journal of Cardiology* 2016;218:150-157
- Oude Lansink. Extracorporeal life support for cardiac and respiratory failure in adults in the intensive care unit in the Netherlands. Indications for ECLS and requirements for an ECLS centre. *Neth J Crit Care* 2016;24(4):24-7
- Farmakis. Levosimendan beyond inotropy and acute heart failure: Evidence of pleiotropic effects on the heart and other organs: An expert panel position paper. *Int J Cardiol* 2016;222:303-312
- Møller. Scandinavian SSAI clinical practice guideline on choice of first-line vasopressor for patients with acute circulatory failure. *Acta Anaesthesiologica Scandinavica* 2016;60(10):1347–1366



The Best Guidelines: RESPIRATORY

- Davidson. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. *Thorax* 2016;71:ii1-ii35
- Claesson. Scandinavian clinical practice guideline on fluid and drug therapy in adults with acute respiratory distress syndrome. *Acta Anaesthesiologica Scandinavica* 2016;epublished March 16th
- Hellyer. The Intensive Care Society recommended bundle of interventions for the prevention of ventilator-associated pneumonia. *JICS* 2016;epublished April 20th
- Cho. Clinical Practice Guideline of Acute Respiratory Distress Syndrome. *Korean J Crit Care Med.* 2016 May;31(2):76-100
- Kalil. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016;epublished July 14th
- Frerichs. Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the TRanslational EIT developmentNt stuDY group. *Thorax* 2016;epublished September 5th
- Bein. S2e guideline: positioning and early mobilisation in prophylaxis or therapy of pulmonary disorders : Revision 2015: S2e guideline of the German Society of Anaesthesiology and Intensive Care Medicine (DGAI). *Anaesthesist* 2015;64 Suppl 1:1-26
- Cho. Clinical Practice Guideline of Acute Respiratory Distress Syndrome. *Tuberc Respir Dis (Seoul)* 2016;79(4):214-233

The Best Guidelines: GI & NUTRITION

- Tilsed. ESTES guidelines: acute mesenteric ischaemia. *European Journal of Trauma and Emergency Surgery* 2016;epublished January 28th
- Strate. ACG Clinical Guideline: Management of Patients With Acute Lower Gastrointestinal Bleeding. *Am J Gastroenterol* 2016;111:459-474
- Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) *JPEN J Parenter Enteral Nutr* 2016;40(2):159-211
- Greenberg. Clinical practice guideline: management of acute pancreatitis. *Can J Surg* 2016;59(2):128-140

The Best Guidelines: HEPATOBILARY

- Shawcross. How to diagnose and manage hepatic encephalopathy: a consensus statement on roles and responsibilities beyond the liver specialist. Eur J Gastroenterol Hepatol 2016;28(2):146-52
- Coccolini. WSES classification and guidelines for liver trauma. World J Emerg Surg 2016;11:50

The Best Guidelines: RENAL

- Ichai. Acute kidney injury in the perioperative period and in intensive care units (excluding renal replacement therapies). Ann Intensive Care. 2016;6(1):48
- Ostermann. Patient Selection and Timing of Continuous Renal Replacement Therapy. Blood Purif 2016;42:224-237
- Bagshaw. Precision Continuous Renal Replacement Therapy and Solute Control. Blood Purif 2016;42:238-247
- Cerdá. Role of Technology for the Management of AKI in Critically Ill Patients: From Adoptive Technology to Precision Continuous Renal Replacement Therapy. Blood Purif 2016;42:248-265
- Murugan. Precision Fluid Management in Continuous Renal Replacement Therapy. Blood Purif 2016;42:266-278

The Best Guidelines: ENDOCRINE

- Satoh. 2016 Guidelines for the management of thyroid storm from The Japan Thyroid Association and Japan Endocrine Society (First edition). Endocr J 2016;epublished October 15th

The Best Guidelines: METABOLIC

- People's Liberation Army Professional Committee of Critical Care Medicine. Expert consensus on standardized diagnosis and treatment for heat stroke. Mil Med Res 2016;3:1

The Best Guidelines: HAEMATOLOGY

- Antithrombotic Therapy for VTE Disease : CHEST Guideline and Expert Panel Report. Chest 2016;epublished January 7th
- Klein. AAGBI guidelines: the use of blood components and their alternatives 2016. Anaesthesia 2016;71(7):829-842
- Squizzato. Supportive management strategies for disseminated intravascular coagulation An international consensus. Thromb Haemost 2016;115(5): 896-904
- Carson. Clinical Practice Guidelines From the AABB Red Blood Cell Transfusion Thresholds and Storage. JAMA 2016;316(19):2025-2035

The Best Guidelines: SEPSIS

- Pappas. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62(4):e1-e50
- McGill. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. Journal of Infection 2016;72:405-438
- Barlam. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016;e62(10):e51-e77
- Thwaites. Recommendations for infection management in patients with sepsis and septic shock in resource-limited settings. Sepsis in resource-limited settings—expert consensus recommendations group of the European Society of Intensive Care Medicine (ESICM). Intensive Care Med (2016) 42: 2040-2042
- NICE UK. Sepsis: recognition, diagnosis and early management. NICE 2016;epublished July
- Zhang. The Society for Translational Medicine: clinical practice guidelines for diagnosis and early identification of sepsis in the hospital. J Thorac Dis 2016;8(9):2654-2665
- Ye. Therapeutic drug monitoring of vancomycin: a guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. J Antimicrob Chemother 2016;71(11):3020-3025



The Best Guidelines: TRAUMA

- NICE. Spinal injury: assessment and initial management. NICE 2016;epublished February
- Rossaint. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Critical Care 2016;20:100
- Perlman. A recommended early goal-directed management guideline for the prevention of hypothermia-related transfusion, morbidity, and mortality in severely injured trauma patients. Crit Care 2016;20(1):107
- Tran. Western Trauma Association Critical Decisions in Trauma: Management of pelvic fracture with hemodynamic instability—2016 updates. J Trauma 2016;81(6):1171-1174
- NICE. Major trauma: service delivery. NICE 2016;epublished February
- NICE. Major trauma: assessment and initial management. NICE 2016;epublished February

The Best Guidelines: BURNS

- ISBI Practice Guidelines for Burn Care. Burns 2016;42:953-1021

The Best Guidelines: TOXICOLOGY

- St-Onge. Experts Consensus Recommendations for the Management of Calcium Channel Blocker Poisoning in Adults. Crit Care Med 2016;epublished October 3rd

The Best Guidelines: PAEDIATRICS

- Brissaud. Experts' recommendations for the management of cardiogenic shock in children. Annals of Intensive Care 2016;6:14
- Guideline: Updates on Paediatric Emergency Triage, Assessment and Treatment: Care of Critically-Ill Children. Geneva: World Health Organization; 2016
- Harris. Clinical recommendations for pain, sedation, withdrawal and delirium assessment in critically ill infants and children: an ESPNIC position statement for healthcare professionals. Intensive Care Med 2016;42(6):972-986



The Best Guidelines: MISCELLANEOUS

- Levitov. Guidelines for the Appropriate Use of Bedside General and Cardiac Ultrasonography in the Evaluation of Critically Ill Patients—Part II: Cardiac Ultrasonography. *Critical Care Med* 2016;44(6):1206–1227
- Kon. Shared Decision Making in ICUs: An American College of Critical Care Medicine and American Thoracic Society Policy Statement. *Crit Care Med* 2016;44(1):188-201
- Moss. A Critical Care Societies Collaborative Statement: Burnout Syndrome in Critical Care Health-care Professionals. A Call for Action. *Am J Respir Crit Care Med* 2016;194(1):106-113
- Myburgh. End-of-life care in the intensive care unit: Report from the Task Force of World Federation of Societies of Intensive and Critical Care Medicine. *J Crit Care* 2016;34:125-130
- Nates. ICU Admission, Discharge, and Triage Guidelines: A Framework to Enhance Clinical Operations, Development of Institutional Policies, and Further Research. *Crit Care Med* 2016;44(8):1553-1602
- Bjoern. Recommended practice for out-of-hospital emergency anaesthesia in adults: Statement from the Out-of-Hospital Emergency Anaesthesia Working Group of the Emergency Medicine Research Group of the German Society of Anaesthesiology and Intensive Care. *Eur J Anaesthesiol* 2016;33:1–17
- Amin. The Intensive care unit specialist: Report from the Task Force of World Federation of Societies of Intensive and Critical Care Medicine. *J Crit Care* 2016;35:223-228
- Kon. Defining Futile and Potentially Inappropriate Interventions: A Policy Statement From the Society of Critical Care Medicine Ethics Committee. *Crit Care Med* 2016;44(9):1769–1774
- Hu. Consensus development of cortencies in intensive and critical care medicine training in China. *Critical Care* 2016;20:330
- Major. Surviving critical illness: what is next? An expert consensus statement on physical rehabilitation after hospital discharge. *Critical Care* 2016;20:354
- Hossfeld. Recommended practice for out-of-hospital emergency anaesthesia in adults: Statement from the Out-of-Hospital Emergency Anaesthesia Working Group of the Emergency Medicine Research Group of the German Society of Anaesthesiology and Intensive Care. *Eur J Anaesthesiol* 2016;33:881-897
- Marshall. What is an intensive care unit? A report of the task force of the World Federation of Societies of Intensive and Critical Care Medicine. *J Crit Care* 2017;37:270–276







Critical Care Reviews Book 2017

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critical care trials of 2016



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