



# Critical Care Reviews Book 2018

The Best Critical Care Trials of 2017



Critical Care  
Reviews



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## **About**

The Critical Care Reviews Book 2018 seeks to summarise, critique and put in context the best critical care trials of 2017. Five intensivists working in Northern Ireland have spent the past year writing this year's 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 once again been very generously sponsored by the REVIVE charity of the Regional Intensive Care Unit at the Royal Victoria Hospital in Belfast, where four 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](http://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](mailto:rob@criticalcarereviews.com)

Chris Gowers, Ulster Hospital Dundonald, Belfast  
Dominic Trainor, Royal Victoria Hospital, Belfast  
Peter McGuigan, Royal Victoria Hospital, Belfast  
Chris Nutt, Royal Victoria Hospital, Belfast  
Rob Mac Sweeney, Royal Victoria Hospital, Belfast

Belfast,  
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### **Disclaimer:**

This book aims to summarise the major critical care trials of 2017. 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.

## Foreword

Because of the complex nature of critical illness, the variability of host response to injury, and the presence of important treatment indication biases, experimental designs including the randomised clinical trial (RCT) are absolutely necessary in advancing the science of critical care medicine. Randomisation with allocation concealment is the key measure that eliminates the selection bias around clinicians' daily treatment decisions, which makes the analysis of observational data fraught with challenges. The chance at play in randomisation will often (but not always) also help balance known and unknown confounders between groups.



At the same time, RCTs are not absolute. The same factors that make RCTs necessary also make them challenging to interpret and apply to clinical practice. Even if one were able to keep track of all the new trials that are emerging, it is not enough to simply read the abstract (or more extremely, just the conclusion of the abstract). Understanding the circumstances of any trial is vital – inclusion/exclusion criteria, non-inclusion of eligible patients, complex protocols, protocol adherence, and heterogeneity of treatment effect and many other factors all may fundamentally change how we interpret a trial result. It is in this context that the Critical Care Reviews Book comes into its own. Each trial receives a thorough 'journal club' treatment provided by the reviewing team.

Ranging across the spectrum of critical care medicine, the authors have selected their take on the most important and influential trials of the year. Much more than a simple summary or abstract, they provide content, critique, and context for each trial. For areas outside of one's special expertise this provides an invaluable framework to add new knowledge; meanwhile for areas where one knows the literature inside and out it serves as a launching pad for discussion and further debate. After all, where our thoughts and beliefs end up after the incremental addition of new estimates generated from a RCT depends not only on the magnitude and precision of those estimates, but also very much on where our prior beliefs were fixed. I believe the Critical Care Reviews 2018 book and the meeting in Belfast in January 2018 will both serve to enhance our shared discussion of how to interpret new science in our field.

### Niall Ferguson

Professor Niall Ferguson MD, FRPCPC, MSc

Professor, Interdepartmental Division of Critical Care Medicine; University of Toronto

Senior Scientist, Toronto General Research Institute

Critical Care Lead, Toronto Central Local Health Integration Network

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# **Section 1: The Best Critical Care Trials of 2017**



# Neuro Trials



## MoDUS

**Page VJ, Casarin A, Ely EW, Zhao XB, McDowell C, Murphy L, McAuley DF. Evaluation of early administration of simvastatin in the prevention and treatment of delirium in critically ill patients undergoing mechanical ventilation (MoDUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2017;5(9):727-737**

### Introduction

As defined by *Diagnostic and Statistical Manual of Mental Disorders* (5th edition), delirium is a state of acute fluctuating brain dysfunction with disturbance of consciousness and altered cognition.<sup>1</sup> It occurs in the setting of many critical illnesses and is a highly prevalent problem in the ICU, with an incidence of 32%.<sup>2</sup> Delirium is associated with a doubling of short-term mortality risk, as well as increases in the duration of mechanical ventilation, length of ICU and hospital stay, a requirement for nursing home care upon discharge from hospital, and progression to the development of dementia.<sup>2</sup>

Neuroinflammation is an important pathological process contributing to the acute brain dysfunction of delirium;<sup>3</sup> therefore, it is logical an anti-inflammatory intervention with the ability to cross the blood brain barrier could impact this condition. Statins are widely used for their cholesterol lowering effects, via the inhibition of the conversion of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) into L-mevalonate, by blocking the enzyme HMG-CoA reductase. In addition, this class of agents also induces post-transcriptional modifications of isoprenoid intermediates downstream of mevalonate, resulting in various anti-inflammatory effects. These anti-inflammatory effects also occur in the brain, where statins have been reported to affect neuroinflammation, blood brain barrier injury, neuronal apoptosis, ischemia and hemorrhage, and microglial activation.<sup>4</sup>

To date, there have been no prospective randomised controlled trials investigating statins in delirium.

### Synopsis

The MoDUS trial investigated the early administration of simvastatin, as both a prophylactic and therapeutic agent, for delirium in the ICU, as well as examining various biological mechanisms of statins in critical illness-related delirium. This was an investigator initiated, single centre, parallel group, randomised, double-blind, placebo-controlled, superiority phase II trial, which took place in Watford General Hospital, England, between February 2013 and July 2016. Critically ill adults requiring mechanical ventilation within 72 hours of ICU admission were eligible. Trial specific exclusion criteria included a creatine kinase (CK) level elevated 10-fold above normal, alanine

transaminase (ALT) elevated 8-fold above normal, use of hepatic enzyme inhibitors, such as itraconazole and amiodarone, uncomplicated elective surgery, an expected ICU admission of less than 48 hours, severe renal or liver impairment, recent or current statin therapy, and contraindication to enteral drug administration.

After consent was obtained from the patient, family member or legal representative, patients were randomised and allocated into the intervention group or control group. Simvastatin or placebo tablets were packaged in identical opaque containers. The indistinguishable tablets were crushed by pharmacy staff and administered enterally by the bedside nurse. Patients received 80 mg of simvastatin or placebo, with clinical and research staff blinded to the study drug administered. The first administration was to occur within 4 hours of randomisation with all subsequent once-daily doses to be given at midday. Study drugs were continued until ICU discharge, day 28, or muscle or liver injury, defined as 10- and 8- fold elevations of creatine kinase or alanine aminotransferase, respectively.

Baseline demographic and clinical data were recorded, as was the risk of developing delirium in the ICU, as measured by the PRE-DELIRIC prediction model. Delirium screening was performed by the bedside nurse at least twice per 12 hour period and whenever there was a change in neurological state, using the Confusion Assessment Method-ICU (CAM-ICU). A patient was considered to be delirious if they had a Richmond Agitation-Sedation Scale (RASS) score of -2 to 4 and had a positive CAM-ICU test. Patients were sedated with infusions of propofol and fentanyl, targeting a RASS score of 0 to -1 (lightly sedated), unless otherwise clinically indicated. Agitation was managed in a protocolised fashion, using haloperidol, olanzapine and/or midazolam. Weaning was also protocolised and all patients were mobilised as able.

The primary outcome was the number of days alive and free of both delirium and coma at day 14 post randomisation. Secondary outcomes included delirium- and coma- free days at day 28, ventilator-free days at day 28, 6 month mortality, length of both ICU and hospital stay and safety, as described by elevated CK and ALT plasma levels, and other adverse events. Cognition was assessed at six months with the Brief Test of Adult Cognition by Telephone (BTRACT).

The sample size was calculated based on both the Awakening and Breathing Controlled (ABC) trial<sup>5</sup> data, where the control group had a median delirium-free and coma-free days of 10 at day 28, and the Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU) Study,<sup>6</sup> which reported a standard deviation of 4.1 days for this outcome at day 14. A sample size of 128 (64 per group) would have 80% power to detect a difference of two delirium-free and coma-free

days at day 14 at a 5% significance level. Allowing for a 10% attrition rate, this sample size increased to 142.

1,164 patients were screened and 142 recruited and randomised. The main reasons for exclusion were current or recent statin therapy (n = 341), an expected ICU duration of less than 48 hours (n = 157), likely withdrawal of active therapy expected (n = 154), and lack of consent (n = 104). Three patients (statin group 2 and control group 1) withdrew from the study and were not included in the secondary analyses but permitted use of their data for the primary outcome.

Groups were similar at baseline, having mean ages of 62 and APACHE II scores of 17, although more men were allocated to the interventional group (45 vs. 26). The most common reasons for admission to the ICU were pneumonia (n = 63), sepsis or ARDS or both (n = 41), COPD (n = 10) and drug overdose (n = 9). The frequency of alcohol abuse was also comparable at approximately 20%. The risk of developing delirium, as measured by the PRE-DELIRIC score, was also comparable, at approximately 25% in both groups. This risk of developing delirium was similar between groups when broken down by medical speciality (surgical  $\approx$  27%, medical  $\approx$  70%, trauma  $\approx$  0.5% and neurosciences  $\approx$  5%). RASS scores were equally alike between groups at baseline. The percentage of CAM-ICU positive patients was identical (n = 56, 79%) in each group. Doses of fentanyl were comparable at study entry, although the propofol dose was slightly lower in the statin group (700 mg vs. 821.5 mg).

All recruited patients received at least one dose of the study drug. The mean (SD) number of days on treatment were: statin, 7.9 (6.6) and control, 10.1 (7.8). There was no difference in the primary outcome of days alive and free of delirium and coma at day 14; statin group, 5.7 (5.1) versus control group, 6.1 (5.2); difference, 0.4; 95% CI, -1.3 to 2.1; P = 0.66. This equality was also seen at day 28: statin group, 14.3 (11.2) vs. control group, 15.4 (10.9); difference 1.1; 95% CI, -2.6 to 4.7; P = 0.56. There were no differences (statin vs. control) in the mean incidences of delirium (93% vs. 94%), days in delirium to 14 days (5.6 vs. 5.5), days in delirium to 28 days (6.4 vs. 6.8), days in coma to 14 days (1.0 vs. 0.9) and days in coma to 28 days (1.1 vs. 1.1). Ventilator-free days at day 28 did not differ (13.7 vs. 15.5), nor did organ-failure-free days at day 28 (14.3 vs. 15.7) and 6 month all-cause mortality (42% vs. 31%). Length of hospital stay until death or discharge was nearly identical at 20 days each. There was also no difference in cognition at 6 months.

## Critique

The strengths of the MODUS trial are the excellent efforts to identify delirium, including the high number of CAM-ICU measurements per day, the requirement for four negative CAM-ICU assessments for a patient to be considered delirium free, as well as RASS-

targeted sedation, a weaning protocol, and mobilisation as standard. As a small, single centre trial, generalisability is an issue, as are the change in eligibility criteria during the trial (eGFR changed from 30 to 15 ml/min ), the choice of an accumulating analgesic in fentanyl, the absence of a pain score, and the inherent limitation of CAM-ICU, a binary tool, to detect delirium on a spectrum, including sub-syndromal delirium.

The incidence of delirium, at over 90% in both groups, is extremely high in comparison with other trials. Whether this is a covert phenomenon largely missed elsewhere, but identified in Watford due to their ingrained delirium focus, is unclear. Despite such a high incidence of delirium, and thus a great opportunity to identify a true anti-delirium effect from simvastatin, no effect was seen. As with any trial, the question emerges as to whether the drug was truly ineffective or whether the trial methodology was too blunt to expose this effect.

The same group of investigators also published the HOPE-ICU trial in 2013, investigating haloperidol for the prevention and treatment of delirium in the ICU.<sup>7</sup> MoDUS was largely based on the same methodology, down to the power calculation, but substituted simvastatin for haloperidol. Unfortunately, by replicating an earlier trial methodology, many of the limitations of the HOPE-ICU trial were inherited by MoDUS, specifically the combined prophylactic and therapeutic nature of the trial and the issue with censoring.

The primary outcome of days alive and free from both delirium and coma is an unusual choice. It is a composite of three outcomes – survival, delirium and coma. A patient who never suffered delirium or coma, yet died within 28 days, perhaps from a complication from their original illness, such as delayed cerebral ischaemia after a subarachnoid haemorrhage, would receive a score of zero. Clearly, such a patient, despite not having been delirious or comatose, scoring zero delirium- or coma-free days sheds little light on the efficacy of simvastatin for delirium.

Paradoxically, a composite endpoint such as this primary endpoint risks being underpowered. If simvastatin was efficacious for either the prevention or treatment of delirium, but not for the other, then the second outcome only serves to dilute the signal of the first. The addition of mortality further confuses the issue and adds little to the delirium focus of the trial.

Also, whether coma and delirium form two sides of a spectrum of neurological dysfunction is unproven.<sup>8</sup> Coma is a failure of the reticular activating system to initiate consciousness. Delirium, a toxic or metabolic encephalopathy, is a cognitive disorder rather than a consciousness disorder. The relationship between these two pathologies remains undefined and whether they should be combined into a composite outcome is

equally unclear. Regardless of the choice of primary outcome, the investigators helpfully report death, days in delirium and days in coma separately, allowing clinicians to draw their own conclusions.

CAM-ICU is a very commonly used delirium screening tool, but is sensitive to the level of sedation, with deeper sedation, RASS scores of -2 and -3, associated with positive delirium assessments, which resolve with lightening of sedation.<sup>9,10</sup> Although patients with a RASS score of -3 were classified as being comatose in the MODUS trial, those with levels of -2 were eligible for being classified as being delirious.

Statins have been studied in several acute critical care conditions over the past decade, including the commonly investigated syndromes of ARDS and sepsis. To date, all trials demonstrated no efficacy against placebo. Simvastatin is known to have anti-inflammatory effects which penetrates the blood-brain barrier to work centrally. Simvastatin was administered for a mean of 8 days, a period long enough to have a pharmacological effect, as evidenced by the lower cholesterol level, yet had no effect on delirium prevention or treatment. Interestingly, the intervention had little effect on serum CRP, a finding seen in other statin trials,<sup>11,12</sup> which collectively question the biological premise underpinning the investigation of statins as inflammatory modulators in the critically ill. Also, whether delirium, a syndrome demonstrating the manifestation of an underlying brain dysfunction, should be the therapeutic target, or the actual pathological process causing the dysfunction, remains unanswered. This approach may be akin to limiting a tachycardia with a beta blocker rather than treating the sepsis driving the heart rate.

### **Where this sits in the body of evidence**

The American randomised controlled SAILS (Statins for Acutely Injured Lungs from Sepsis) trial<sup>13</sup> incorporated an ancillary study<sup>14</sup> evaluating whether rosuvastatin reduced ICU-associated delirium and improved subsequent cognitive function. The primary study was stopped for futility after 745 of a planned 1000 patients were recruited. The delirium study enrolled 272 patients with sepsis-associated acute respiratory distress syndrome (ARDS), who received either rosuvastatin (40 mg loading dose followed by 20 mg daily) or placebo for up to 28 days. Delirium was screened for with the CAM-ICU method. 72% of patients assessed had delirium. There were no differences in the primary endpoint of ICU delirium days {statins, 34% (SD 30%) versus placebo, 31% (29%); HR, 1.14; 95% CI, 0.92 to 1.41; P = 0.22} or secondary endpoints of cognitive impairment at 6 months {statins, 36% versus placebo, 38% (treatment effect, 0.93; 95% CI, 0.39 to 2.22; P = 0.87)} and 12 months {30% versus 28%; treatment effect, 1.1; 95% CI, 0.5 to 2.6; P = 0.82}.

HOPE-ICU was a single-centre, randomised, placebo-controlled trial investigating haloperidol (2.5 mg 8 hourly ) for the prevention and treatment of delirium in 142 critically ill patients receiving mechanical ventilation.<sup>7</sup> Despite a mean number of study drug administrations of approximately 16 per patient, there was no difference in the primary outcome of days alive, without delirium, and without coma; haloperidol, median 5 (IQR 0 - 10) versus placebo, 6 (0 - 11); difference, -0.48; 95% CI, -2.08 to 1.21; P = 0.53. Similarly, there were no differences in any secondary outcomes.

One prospective multi-centre and three retrospective single-centre observational studies examining statins in delirium have reported conflicting results.<sup>15</sup>

The international STASH trial randomised 803 patients with aneurysmal subarachnoid haemorrhage to receive either simvastatin 40 mg or placebo once daily.<sup>16</sup> Groups were similar at baseline, with over 70% having World Federation of Neurosurgical Societies grade 1 or 2 haemorrhages. One-third of patients were surgically clipped. Simvastatin did not demonstrate efficacy in any endpoint, including the primary outcome of having a favourable outcome, modified Rankin Scale 0 – 2, adjusted OR, 0.97; 95% CI, 0.75 to 1.25; P = 0.809. The degree of compliance with administration of the study drug did not affect outcome.

The Irish Critical Care Clinical Trials Group HARP 2 trial compared simvastatin with placebo in 540 mechanically ventilated patients with ARDS.<sup>11</sup> Both groups were well matched at baseline. Although simvastatin 80 mg once daily was effective in reducing serum cholesterol levels, it had no effect on either the primary outcome of ventilator-free days (simvastatin, 12.6 ± 9.9 versus placebo, 11.5 ± 10.4; mean difference, 1.1 days; 95% CI, -0.6 to 2.8; P = 0.21) or secondary endpoints, including non-pulmonary organ failure-free days, mean duration of both ICU and hospital stay, or 28-day mortality (22.0% versus 26.8%).

The ARDSnet SAILS trial was another statins in ARDS trial, which took place in the USA.<sup>13</sup> 745 patients with sepsis-associated ARDS were randomised to receive either rosuvastatin (40 mg loading dose plus 20 mg daily thereafter) or placebo. Patients received study drugs for an average of 9 days, with median peak and trough rosuvastatin levels being 7.3 ng/ml and 2.4 ng/ml, respectively. There was no difference in the primary outcome of death in health care facility until day 60, (rosuvastatin group, 28.5% versus placebo group, 24.9%), or secondary endpoints, including ventilator-free days (15.1 versus 15.1), ICU-free days (14.3 versus 14.4). Of concern, rosuvastatin administration resulted in fewer days free of hepatic- (10.8 vs. 11.8) or renal- failure (10.1 vs. 11.0) free days.



The ANZICS Clinical Trials Group completed a stratified, phase II randomised controlled trial, comparing atorvastatin 20mg daily with placebo, in 250 critically ill patients with sepsis.<sup>12</sup> Although there was no difference in the primary outcome of plasma IL-6 levels, the strata of patients usually receiving statins prior to their critical illness, had a lower IL-6 level and improved 28-day mortality (5% vs. 28%; P = 0.01), than statin naive patients. This mortality benefit lost statistical significance at 90 days (11% vs. 28%; P = 0.06).

### **Should we implement this into our practice?**

No. MODUS does not provide evidence for the routine introduction of statins in the management of ICU delirium. These results are in keeping with other ICU trials investigating statins for a range of conditions.

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## DESIRE

**Kawazoe Y, Miyamoto K, Morimoto T, Yamamoto T, Fuke A, Hashimoto A, et al. Effect of Dexmedetomidine on Mortality and Ventilator-Free Days in Patients Requiring Mechanical Ventilation With Sepsis: A Randomized Clinical Trial. JAMA 2017;317(13):1321–8**

### Introduction

Prospective cohort studies have demonstrated that delirium in mechanically ventilated patients is an independent predictor of 6-month mortality, length of hospital stay and cognitive dysfunction.<sup>1,2</sup> The prevention of ICU delirium with dexmedetomidine, a selective  $\alpha_2$ -adrenoceptor agonist licensed for use as a sedative agent in the ICU setting, has been an active area of research. Dexmedetomidine reduces the incidence and duration of delirium in comparison with benzodiazepines,<sup>3-6</sup> and also shortens the length of mechanical ventilation.<sup>4,7</sup> A meta-analysis has shown that dexmedetomidine infusion also results in a lower rate of delirium and shorter ICU stay when compared to propofol.<sup>8</sup>

In 2007, the MENDS trial compared lorazepam infusion to dexmedetomidine in 106 mechanically ventilated patients and demonstrated a reduction in delirium.<sup>3</sup> In an a-priori subgroup of patients with sepsis (n = 63), those treated with dexmedetomidine had a lower mortality, a greater number of days free from delirium or coma and more ventilator-free days.<sup>9</sup> There are a number of proposed mechanisms by which dexmedetomidine may improve outcomes in sepsis other than through a reduction in delirium. For example, esmolol reduces noradrenaline requirements and mortality in sepsis; dexmedetomidine similarly down regulates catecholamine activity.<sup>10</sup> In a lipopolysaccharide model of sepsis, rats treated with dexmedetomidine had less acute kidney injury and a reduction in inflammatory cytokines.<sup>11</sup> Dexmedetomidine may also have positive effects in innate immunity through reduced apoptosis, improved macrophage phagocytosis and enhanced bacterial clearance.<sup>9</sup> On this basis, the DESIRE trial (DEXmedetomidine for Sepsis in ICU Randomized Evaluation trial) hypothesised that dexmedetomidine may improve outcomes in critically ill patients with sepsis.

### Synopsis

This investigator initiated, multi-centre, open-label, randomised controlled trial examined whether dexmedetomidine would reduce mortality and ventilator-free days in critically ill patients with sepsis who required mechanical ventilation. Hospira, the supplier of dexmedetomidine in Japan, participated in the design of this study and provided a research grant to Wakayama Medical University but had no further input into the study.

Eight ICUs in Japan recruited adults with sepsis (defined as the presence of systemic inflammatory response syndrome due to infection or acute pancreatitis) and a requirement for invasive or non-invasive mechanical ventilation for > 24 hours. Exclusion criteria included burns, heat stroke, Child-Pugh grade B or C liver disease, acute myocardial infarction, New York Heart Association class 4 cardiac failure, drug or alcohol dependence and severe cognitive impairment.

Patients were randomised in permuted blocks of four to the dexmedetomidine group (sedation with dexmedetomidine at 0.1 to 0.7 µg/kg/h and fentanyl at 0 to 5 µg/kg/h plus additional propofol or midazolam as required) or the control group (sedation with propofol 0 to 3 mg/kg/h, midazolam 0 to 0.15 mg/kg/h, and fentanyl 0 to 5 µg/kg/h). The sedation target was a Richmond Agitation-Sedation Scale (RASS) score of 0 during the day and -2 at night. Stratification was based on emergency surgery, chronic obstructive pulmonary disease, and presence of severe soft tissue infection, such as necrotizing fasciitis (due to the likelihood of needing a prolonged ICU stay).

The co-primary outcome measures were 28-day mortality and ventilator-free days to day 28. There were 16 secondary outcomes, including RASS score, Confusion Assessment Method for ICU Patients (CAM-ICU) score, ICU and hospital length of stay. The rate of well controlled sedation (RASS score between -3 and +1 throughout 1 day spent in the ICU) was evaluated post hoc.

The power calculation estimated that 172 patients would be needed to detect a 20% difference in 28-day mortality between the two groups with 80% power and a 2-sided P value of 0.05. This was based on an assumed 20% mortality in the dexmedetomidine group and 40% mortality in the control group, with these values being derived from the MENDS trial.<sup>3,9</sup> To allow for a 15% drop out it was planned to enrol 200 patients. Both co-primary outcomes were required to reach statistical significance for the null hypothesis to be rejected. Analyses were carried out using an intention-to-treat principle. Time-to-event data were censored at 28 days.

In total, 203 patients were assessed for eligibility, with just two excluded. 100 were randomised to the dexmedetomidine group (one patient was discharged from ICU before receiving dexmedetomidine) and 101 to the control group (six patients received dexmedetomidine at the discretion of the treating physician). The groups were well balanced at baseline, with a typical patient being a male in their late 60s with an APACHE II score of 22 to 23. Circulatory shock {defined as the presence of ≥ 3 components of the cardiovascular sequential organ failure assessment (SOFA) score} was present in 69% of patients. The commonest sites of infection were abdomen (39%) and thorax (36%).

In days 1 - 7 there was no difference in the number of patients using fentanyl or the total dose given (with a typical dose being 600 mcg/day). In keeping with the sedation protocol, the number of patients treated with propofol and the dose used was significantly higher in the control group on days one to six, but not day seven. Similarly, the number of patients who received midazolam, and the dose used, was statistically higher in the control group on days one to five and day seven, but not day six. However, the median dose of midazolam administered was zero in both groups on days one to seven.

There was no difference in either of the co-primary outcome measures. The 28-day mortality in the dexmedetomidine group was 22.8% compared with 30.8% in the control group (HR, 0.69; 95% CI, 0.38 to 1.22; P = 0.20). In a subgroup analysis of 104 patients with an APACHE II score of  $\geq 23$  (which represented the median APACHE II score), those treated with dexmedetomidine had a lower mortality (HR, 0.39; 95% CI, 0.16 to 0.91; P = 0.03). There was no difference in the number of ventilator-free days in the first 28 days; 20 (IQR 5 to 24) vs. 18 (IQR, 0.5 to 23) in the dexmedetomidine and control groups, respectively (P = 0.20).

There was no difference in the rates of positive CAM-ICU score; 44% vs. 45% in the dexmedetomidine and control groups, respectively (P = 0.94). Post hoc, the rate of well-controlled sedation for each day was significantly higher in patients treated with dexmedetomidine (range 17% to 58%) than those treated with standard care (20% to 39%) (P = 0.01). There was no difference in the number of days free from both delirium and coma (P = 0.17). With the exception of C-reactive protein (CRP), there was no difference in any of the secondary outcome measures, including median length of ICU stay (P = 0.43), daily SOFA score on days 1, 2, 4, 6 and 8 or adverse events.

## Critique

DESIRE was a well conducted, although small trial, attempting to demonstrate an enthusiastic mortality effect size of 20%. Methodologically, the trial has a number of strengths. The groups separated well, with good differences in administered propofol doses and little cross over with dexmedetomidine administration. This suggests dexmedetomidine had a beneficial sedative effect and implies good internal validity. However, it must borne in mind that this was an open label study and clinicians may have unintentionally used a lower dose of propofol as a result, raising the question as to why the investigators chose an open label design when similar studies have successfully blinded dexmedetomidine.<sup>3,4,6,7</sup> In using CAM-ICU, a widely used and well validated delirium screening tool was chosen.<sup>12</sup>

The standard of care appeared to be high, as the patient outcomes are typical of a cohort of critically ill patients with sepsis. The incidence of circulatory shock (69%) and median APACHE II scores (23 and 22 in the dexmedetomidine and control group, respectively) are higher than those seen in a recent trial examining early goal directed therapy in sepsis.<sup>13</sup> The observed 28-day mortality rate (22.8% to 30.8%), number of ventilator-free days and number of days free from delirium or coma were similar to other large studies.<sup>1,3,13</sup>

Although the trial recruited the intended 201 patients to achieve power, it is still smaller than a number of other recent trials examining the effect of dexmedetomidine.<sup>4,6</sup> DESIRE was powered to detect a 20% reduction in mortality, based on a subgroup analysis from the relatively small MENDS trial. Smaller trials potentially amplify between-group differences, an effect which may be compounded when followed with another small trial. A 20% absolute reduction in mortality appears overly optimistic.<sup>14</sup> A statistically non-significant difference of 8% was seen, largely owing to a lower than expected mortality in the control group. As such, a smaller but clinically relevant mortality difference may have been missed.

In the subgroup analysis of patients with sepsis from the MENDS trial, the observed reduction in mortality was improbably large and the confidence intervals were wide (HR, 0.3; 95% CI, 0.1 to 0.9). Had the investigators chosen a more plausible effect size and planned to recruit a greater number of patients, the trial would have been more robust. To counter this argument, the reduction in mortality seen in the cohort of patients with an APACHE II score  $\geq 23$  in DESIRE (HR, 0.39; 95% CI, 0.16 to 0.91; P = 0.03) was of similar magnitude to that seen in the MENDS trial, where the mean APACHE II score was 30.<sup>9</sup>

There are some points regarding the outcome measures which warrant discussion. The co-primary outcome measure of mortality should be less affected by the open nature of the trial. Decisions to extubate, and hence ventilator-free days can be more subjective. In an effort to obviate this issue, the investigators defined criteria which should be met prior to attempting to wean the patient from ventilation, including absolute PaO<sub>2</sub> values, ventilator settings and rapid shallow breathing index values. Other measures, such as CAM-ICU and RASS, despite their excellent inter-rater reliability, may have been impacted by the open label nature of the study.<sup>12</sup> Furthermore, it is unclear how often these assessments of agitation and delirium were made and whether training was given in CAM-ICU testing. Among the large number of secondary outcomes, there were few significant between-group differences. With the exception of CRP, these were defined post hoc.

One potential source of criticism is the low dose of dexmedetomidine used. On day three, the day in which the highest dose of dexmedetomidine was administered, the median dose used was 336 µg (which equates to 0.2 µg/kg/h for a 70 Kg patient). In contrast, the median dose of dexmedetomidine administered in the MENDS trial was 0.74 µg/kg/h (IQR 0.39 to 1.04 µg/kg/h).<sup>3</sup> This low dose may, in part, explain the lack of difference in the rates of delirium as assessed by CAM-ICU. In addition, the investigators postulate that dexmedetomidine may have beneficial cardiovascular effects in sepsis. No data is presented in relation to mean blood pressure, inotrope / vasopressor doses or heart rate (with the exception of incidence of bradycardia, which did not differ between the two groups). It is possible the low dose of dexmedetomidine used did not have a significant cardiovascular effect.

The hypothesis for the DESIRE trial was generated based on an *a priori* subgroup analysis of the MENDS trial.<sup>9</sup> While there is biological rationale for why dexmedetomidine may be beneficial in sepsis, it has also been postulated that benzodiazepines may be harmful in sepsis.<sup>9</sup> However, this trial did not replicate the methodology of the MENDS trial which compared a dexmedetomidine infusion with a lorazepam infusion. Instead the control group was standard care, which included propofol, midazolam and fentanyl at the discretion of the treating clinician. With their potential for accumulation, the role of benzodiazepine infusions in ICU warrants further discussion.

Many of the previous trials which have demonstrated reduced delirium and shorter duration of ventilation when using dexmedetomidine have used continuous benzodiazepine infusion as a comparator.<sup>3,4</sup> It may be that benzodiazepines are harmful as opposed to dexmedetomidine being beneficial. In a large cohort based study, patients treated with propofol only sedation were matched to controls treated with either propofol and midazolam or propofol and lorazepam. The use of a benzodiazepine-based infusion was associated with a 22% to 24% relative increase in mortality, a greater ICU length of stay, prolonged ventilatory dependence and a higher incidence of ventilator-associated pneumonia.<sup>15</sup> In the community setting, a case-control study of almost 35,000 patients demonstrated that benzodiazepine use was associated with an increased risk of developing community-acquired pneumonia (OR, 1.54; 95% CI, 1.42 to 1.67; P < 0.001) and an increased 30-day mortality following pneumonia (HR, 1.22; 95% CI, 1.06 to 1.39; P < 0.001).<sup>16</sup> This appeared to be a class effect, with only chlordiazepoxide failing to demonstrate an association with negative outcomes.

In the DESIRE study, there was a statistically significant higher use of midazolam in the control group. However, the median dose administered on each of the first seven days was zero in both groups (although the upper IQR was higher in the control group). The mean doses of midazolam infused were not presented. As the doses of fentanyl

administered were similar in each group, it could be argued this became a trial of low dose dexmedetomidine versus propofol.

In summary, this open label trial looking at the use dexmedetomidine in sepsis failed to reject the null hypothesis. There are a number of potential explanations for this including the low dose of dexmedetomidine administered, the low use of benzodiazepines in the control group and the potential of a small treatment effect being missed. On this basis a larger study using a higher dose of dexmedetomidine may be warranted. If such a trial is undertaken, it may be appropriate to use a non-benzodiazepine based sedative regimen in a third arm.

### **Where this sits in the body of evidence**

The MENDS trial randomised 106 mechanically ventilated ICU patients to sedation with dexmedetomidine or lorazepam for up to 120 hours, titrated to RASS. 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%,  $P=0.04$ ). There was no difference in the 28-day mortality, 17% vs. 27% in the dexmedetomidine and lorazepam groups, respectively ( $P = 0.18$ ).<sup>3</sup>

An *a priori* subgroup analysis of the MENDS trial examined the effect of dexmedetomidine compared to lorazepam in 63 patients with sepsis. In relation to the primary outcome measure, those treated with dexmedetomidine had a mean 3.2 days (95% CI, 1.1 to 4.9) more free from delirium/coma in the first 12 days. Among the secondary outcomes, those randomised to dexmedetomidine had a significantly lower mortality (HR, 0.3; 95% CI, 0.1 to 0.9), a higher number of delirium-free days and more ventilator-free days than those randomised to lorazepam.<sup>9</sup>

In the SEDCOM trial, Riker et al randomised 375 ICU patients to dexmedetomidine- or midazolam- based sedation. The primary outcome, time spent within target RASS range, was similar between group. 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. v 18.9%;  $P = 0.001$ ).<sup>4</sup>

In a recently published blinded trial conducted in two tertiary ICUs in Beijing, China, 700 ICU patients aged > 65 were randomised to receive prophylactic low dose dexmedetomidine (0.1 µg/kg/hr) or placebo following non-cardiac surgery in an effort to prevent delirium. Patients were assessed twice daily for delirium using the CAM-ICU screening tool. The primary endpoint was the incidence of delirium in the first post-



operative week. This was more common in the placebo-treated group (23% vs. 9%; OR, 0.35; 95% CI, 0.22 to 0.54;  $P < 0.0001$ ). The placebo group had a prolonged median time to extubation (6.9 hrs vs. 4.6 hrs; HR, 1.25; 95% CI, 1.02 to 1.53;  $P = 0.031$ ). This resulted in a clinically insignificant longer median ICU length of stay with placebo of 0.6 hours ( $P = 0.027$ ). There was no difference in hospital length of stay or mortality.<sup>6</sup>

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. 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.<sup>5</sup>

The DahLia trial 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). Median ventilator-free hours (primary outcome) was increased in the dexmedetomidine group (145 vs. 128 hours;  $P = 0.01$ ). Among the 26 secondary outcome measures, almost all demonstrated a signal towards better outcomes in the dexmedetomidine group; delirium resolved more quickly (23 vs. 40 hours;  $P = 0.01$ ), the requirement for antipsychotic medications was reduced, and median ICU length of stay was shorter (-1.0 day; 95% CI, -2.1 to 0.1;  $P = 0.09$ ). Adverse events were rare. Recruitment was halted early after the sponsor declined to extend funding.<sup>7</sup>

### **Should we routinely sedate septic patients requiring mechanical ventilation with dexmedetomidine?**

Not at present. However, as this trial reported a small, statistically non-significant yet clinically relevant difference in mortality, further studies are required.

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## Neonatal Cooling in Hypoxic-Ischaemic Encephalopathy

**Shankaran S, Laptook AR, Pappas A, McDonald SA, Das A, Tyson JE, et al. Effect of Depth and Duration of Cooling on Death or Disability at Age 18 Months Among Neonates With Hypoxic-Ischemic Encephalopathy: A Randomized Clinical Trial. JAMA. 2017;318(1):57–67**

### Introduction

Hypoxic ischaemic encephalopathy (HIE) may occur in infants as a result of intrapartum asphyxia. It can result in death or life long disability, with potentially devastating consequences for patients and their families. The ischaemia / reperfusion injury triggers cellular changes including the depletion of ATP, the release of the excitatory neurotransmitter glutamate and a rise in intracellular calcium, all of which result in the production of free radicals. These processes ultimately result in neuronal necrosis and apoptosis.<sup>1</sup>

Hypothermia has been demonstrated to improve rates of survival free from neurological disability. A landmark trial by Shankaran and colleagues randomised 208 infants with HIE to cooling to 33.5 °C or standard care, which consisted of temperature control to 36.5°C to 37°C. Cooling resulted in a 28% relative risk reduction in rates of death or moderate to severe disability at 18 to 22 months in comparison to standard care.<sup>2</sup> The TOBY trial which ran from 2002 to 2006 randomised infants with HIE to cooling to 33 to 34°C or standard care. Although it did not demonstrate any difference in rates of death or severe disability, there was a reduction in the secondary outcome measures of rates of moderate disability and an increase chance of survival-free from disability with cooling.<sup>3</sup> In 2006, the Neurology Group on Hypoxic-Ischemic Encephalopathy recommended that depth and duration of hypothermia for HIE be investigated. The same group also suggested eligibility criteria for studies into HIE.<sup>1</sup> On this basis a trial examining the effect of different depths and duration of cooling in HIE was undertaken.

### Synopsis

This 2 x 2 factorial design, randomised, controlled trial investigated whether increased depth (32°C) or duration (120 hours) of cooling would further reduce rates of death or disability at 18 months following HIE. Preliminary results of this trial, describing secondary outcome measures, has previously been published.<sup>4</sup> This paper was the first presentation of the primary outcome measure of death or moderate-to-severe disability at > 18 months.

Eligible patients were infants  $\geq$  36 weeks' gestation with HIE who could be enrolled within six hours of birth. Potential cases were identified using the following criteria:

- a cord pH < 7.0 / base deficit > 16 mmol/L in the first hour of life, or
- a cord pH < 7.15 / base deficit 10 - 15.9 mmol/L plus an acute perinatal event, or
- either a 10 minute Apgar score ≤ 5 or a requirement for mechanical ventilation.

Once one of these criteria were met, infants were screened for encephalopathy or seizures using a structured examination and enrolled if present.<sup>4</sup> Exclusion criteria were moribund state, lack of commitment to full treatment, weight < 1,800 g, hypothermia < 32.5°C, major congenital abnormality, or refusal to consent by a physician or caregiver.

Due to the 2 x 2 factorial design, infants could be randomised to one of four cooling groups: 33.5°C for 72 hours, 32.0°C for 72 hours, 33.5°C for 120 hours, or 32.0°C for 120 hours. There was stratification based on study site and degree of encephalopathy. Infants were cooled using a Blanketrol II Hyper-Hypothermia system (Cincinnati Sub-Zero) in conjunction with an oesophageal temperature probe which created a closed loop feedback system. After the intervention period, infants were rewarmed at 0.5°C/h to 36.5°C - 37°C. All other interventions were at the discretion of the treating team.

The primary outcome measure was a composite of death or moderate to severe disability at > 18 months. Severe disability was defined as any of the following: Bayley Scales of Infant Development (BSID) III < 70 (mean 100, SD 15), Gross Motor Function Classification System (GMFCS) level 3 to 5, blindness or hearing loss despite amplification devices (i.e. inability to follow commands despite aids). Moderate disability required the presence of Bayley Scales of Infant Development III 70 - 84 and GMFCS level 2, seizure disorder or hearing loss requiring amplification (Table 1). Secondary outcomes measures included measures of disability, motor and cognitive scores, and mortality following neonatal ICU (NICU) discharge.

Moderate disability	Severe disability
<b><i>Cognitive outcomes</i></b>	
Bayley Scales of Infant Development III <ul style="list-style-type: none"> <li>• 70 - 84 (mean 100, SD 15)</li> </ul>	Bayley Scales of Infant Development III <ul style="list-style-type: none"> <li>• &lt; 70 (mean 100, SD 15)</li> </ul>
<b><i>Functional outcomes</i></b>	
GMFCS level 2 <ul style="list-style-type: none"> <li>• unable to walk but can pull to stand and take steps holding on to furniture</li> </ul>	GMFCS level 3-5 <ul style="list-style-type: none"> <li>• requires hands for sitting support and is unable to crawl</li> <li>• support required for sitting</li> <li>• requires adult assistance to move</li> </ul>

**Table 1. Description of cognitive and functional outcomes**

The investigators assumed that depth or duration of cooling, or both, would reduce the risk of death or moderate-to-severe disability. For each of the four groups, they predicted the incidence of the primary outcome measure, ranging from a maximum of 45% in the group cooled to 33.5°C for 72 hours to a minimum of 25% in the 32.0°C for 120 hours group. In powering the study, it was estimated that 726 infants would be required to give an 80% power to detect a reduction from 37.5% to 27.5% in the primary outcome measure, with either increased depth or duration of cooling. A two sided  $\alpha$  was set at 0.05. There was no adjustment for multiple comparisons.

Over a six year period at 18 US centres, 1,261 infants were screened for eligibility. 747 were not eligible and 150 were not enrolled as either their parents did not consent ( $n = 100$ ), parents were not approached ( $n = 45$ ) or the treating physician refused consent ( $n = 5$ ). Interim analysis was performed after enrolment of the first 50 infants and then every 25 thereafter. The trial was terminated after enrolment of 364 infants on the basis of futility and concerns surrounding in-hospital mortality. Futility analysis was carried out and estimated that the chance of determining a benefit from longer cooling, deeper cooling, or both was  $< 2\%$ .<sup>4</sup>

The 364 recruited infants were randomised as follows; 72 hours of cooling to 33.5°C ( $n = 95$ ), 72 hours of cooling to 32.0°C ( $n = 90$ ), 120 hours cooling to 33.5°C ( $n = 96$ ), or 120 hours of cooling to 32.0°C ( $n = 83$ ). The groups were well balanced with respect to maternal baseline characteristics, duration of ruptured membranes prior to delivery (mean approximately 11 hours), intrapartum complications, rates of emergency caesarean section (63%) and neonatal characteristics. A typical infant had an Apgar scores  $\leq 5$  after 5 minutes, an umbilical cord pH of 6.9, a base deficit of 16 mmol/L and moderate encephalopathy. Approximately one in three infants had seizures and one in four required inotropes. There was excellent separation in the temperatures of the groups.

There was no difference in death or moderate-to-severe disability when 72 hours of cooling was compared to 120 hours of cooling: 31.5% vs. 31.6%, respectively (adjusted relative risk (ARR), 0.92; 95% CI, 0.68 to 1.25;  $P = 0.60$ ). Similarly, there was no difference when 33.5°C was compared to 32°C; 31.9% vs. 31.5% respectively (ARR, 0.92; 95% CI, 0.68 to 1.26,  $P = 0.62$ ). There was a statistically significant interaction between the two groups with respect to the primary outcome measure ( $P = 0.048$ ).

Among the secondary outcome measures, death was more common in the group cooled for 120 hours than 72 hours (ARR, 1.39; 95% CI, 1.02 to 1.90.  $P = 0.04$ ). There was no difference in mortality when cooling to 32°C was compared to 33.5°C (ARR, 1.17; 95% CI, 0.67 to 2.04;  $P = 0.58$ ). When the four groups were compared individually, the Bayesian

model adjusted relative risk of death increased with increasing “dose” of cooling: 32.0°C for 72 hours (ARR, 1.08; 95% credible interval (CrI), 0.74 to 1.59), 33.5°C for 120 hours (ARR, 1.33; 95% CrI, 0.91 to 1.93) and finally 32.0°C for 120 hours (ARR, 1.36; 95% CrI, 0.81 to 2.21). This was in keeping with the preliminary data which had given a signal of harm in the form of increased NICU mortality with increased depth and duration of cooling.

Of the 27 secondary outcomes where P values were quoted, two outcome measures favoured the group cooled for 120 hours: readmissions after hospital discharge (ARR, 0.57; 95% CI, 0.36 to 0.93; P = 0.02) and Bayley III motor score < 70 (ARR, 0.60; 95% CI, 0.36 to 0.98; P = 0.04). This raised concern that increased depth of cooling commuted infants from severe disability to death, resulting in the increased rates of mortality but lower disability seen in the cooling for 120 hours group. There was no difference in any of the secondary outcomes when 33.5°C was compared to 32°C. As there was no adjustment made for multiple comparisons, secondary outcomes should be considered as exploratory.

## Critique

This was a well conducted study. In examining both depth and duration of cooling it addressed an important question where research was needed.<sup>1</sup> The outcome measures of death or moderate to severe disability were relevant to patients and their families. In keeping with previous studies, the investigators used validated tools to measure levels of disability.<sup>2,3,5</sup>

The investigators should be commended for the level of safety measures incorporated in the study design. An independent data and safety monitoring committee (DSMC) reviewed head sonograms for the first 50 infants enrolled and recruitment was paused for a 13 month period whilst a safety analysis was completed. Once no evidence of an increase in cerebral thrombosis or haemorrhage was seen, trial recruitment recommenced with head sonograms performed on the next 50 infants enrolled. After this point the DSMC were happy to proceed without head sonograms. Interim safety analysis was conducted after every 25 neonates were enrolled. A narrative review of in-hospital deaths was conducted at the fourth review. At the eighth review recruitment was ceased due to futility and an emerging trend towards increased mortality with longer, deeper cooling. The investigators took the laudable decision to publish interim results to highlight safety concerns.<sup>4</sup>

In explaining the decision to choose a 2 x 2 factorial design, the investigators stated they assumed “no large statistical interactions between depth and duration of cooling.” It was intended to separately compare the effect of increased depth of cooling and increased

duration of cooling.<sup>4</sup> As altering the depth or duration of cooling merely alters the dose administered, it seems logical that these two interventions would interact. Indeed, this proved to be the case, with a statistically significant interaction seen in relation to the primary outcome measure. With the benefit of hindsight it may have been appropriate to increase the power of this factorial design trial to detect an interaction.<sup>6</sup> Alternatively, a single trial with four parallel groups or two separate trials could have been chosen (although both would have required significantly larger sample sizes). Analogies can be drawn with research into therapeutic hypothermia after cardiac arrest in adults where separate trials into depth and duration have been conducted.<sup>7,8</sup>

Ultimately, the discussion about power calculations to detect an interaction between the groups is moot as the trial was terminated early having recruited approximately half of the 726 infants needed to achieve power. The lack of power is further compounded by the lower than expected incidence of death or moderate-to-severe disability. In three previous major studies this occurred in approximately 45 to 55% of infants who were cooled.<sup>2,3,5</sup> The investigators speculate that the infants enrolled in this trial may not have been as unwell as those in previous trials, as they observed lower rates of severe encephalopathy, seizures and less physiological derangement.<sup>2,4</sup>

This trial examined both depth and duration of cooling. By comparing 72 hours with 120 hours of cooling, it seems biologically plausible that a difference in the primary outcome measure could have been observed. However, the choice of 32°C as a target temperature in comparison to 33.5°C merits exploration. Previous studies into cooling in HIE have compared 33°C to 34°C with 36.5°C to 37.0°C. In these studies, this 3°C to 4°C decrease in temperature resulted in an 8% to 16% absolute reduction in death or disability.<sup>2,3</sup> On this basis, a 1.5°C separation in temperature between the two groups seems small. It was anticipated that over a 72 hour intervention period cooling to 32°C instead of 33.5°C would reduce the likelihood of death or disability to 30% from 45%. On reflection this seems ambitious. It is noteworthy that excellent separation in temperatures was observed between the two groups, yet there was no difference in any of the primary or secondary outcome measures when 32°C was compared to 33.5°C.

In researching the appropriate “dose” of cooling in HIE, the investigators have chosen to compare more profound depths of hypothermia (32°C vs. 33.5°C). The CoolCap trial has shown that selective head cooling using a cap which circulated water at 8°C to 12°C, along with mild systemic hypothermia (target rectal temperature 34 to 35°C), improved outcomes in HIE.<sup>5</sup> In contrast, adult studies investigating the “dose” of cooling following out-of-hospital cardiac arrest (OHCA) have used less aggressive cooling as their intervention. The TTM trial compared therapeutic hypothermia (33°C) with targeted temperature management (TTM, 36°C). The upcoming TTM2 trial is set to compare



therapeutic hypothermia (33°C) with normothermia and early treatment of fever (< 37.8°C) (NCT02908308). Therapeutic hypothermia in infants is associated with an increase in oxygen requirements, acute pulmonary hypertension and bradycardia.<sup>9</sup> This must be balanced with the fact that every 1°C increase in mean temperature > 37.5°C is associated with a four fold increase in death or severe disability in infants with HIE.<sup>10</sup> Therefore TTM, which minimises the physiological consequences of hypothermia whilst avoiding harmful pyrexia, may be a potential area for research in HIE.

In summary this 2 x 2 factorial trial examined the effects of depth and duration of cooling on HIE. As the separation in temperature between the two groups was small, the trial was much more likely to detect a difference due to an increase in duration of cooling. The early termination of recruitment due to concerns over safety and likely futility mean the trial was ultimately underpowered, although unlikely to have shown a difference had it continued. The use of TTM to treat HIE may be an area for future work.

### **Where it sits in the body of evidence**

The trials described below used largely standardised eligibility criteria to identify cases of HIE.<sup>2,3,5</sup> Infants aged  $\geq$  36 weeks gestation were eligible if they met all three of the following preconditions:

- a pH < 7 or base deficit  $\geq$  16 mmol/L at 60 minutes, Apgar score  $\leq$  5 at 10 minutes after birth or ongoing resuscitation at 10 minutes after birth
- lethargy, stupor, or coma indicating a moderate-to-severe encephalopathy plus either hypotonia, abnormal reflexes, weak suck reflex, or seizures
- electroencephalography evidence of seizures or encephalopathy.

The TOBY trial examined the role of cooling in 325 infants with HIE. Infants were randomised within six hours to standard NICU care (which included maintenance of temperature at  $37.0 \pm 0.2^\circ\text{C}$  using an incubator or radiant heater) or NICU care plus cooling to  $33^\circ\text{C}$  to  $34^\circ\text{C}$  for 72 hours. After 72 hours of cooling infants were rewarmed at a rate of  $0.5^\circ\text{C}/\text{h}$ . The primary outcome measure was death or severe disability at 18 months defined as score < 70 for the Mental Development Index component of BSID-II, GMFCS 3 to 5, or cortical blindness. The primary outcome measure occurred in 74 / 163 infants in the cooled group and 86 / 162 of the standard care group (relative risk, 0.86; 95% CI, 0.68 to 1.07; P = 0.17). However, among the secondary outcomes multiple measures demonstrated infants were more likely to survive free from neurological abnormality with cooling (44% vs. 28% in the cooled and non-cooled groups, respectively; RR, 1.57; 95% CI, 1.16 to 2.12; P = 0.003).<sup>3</sup>

A randomised controlled trial examined the effect of whole body cooling in 208 term infants with HIE. Entry criteria were identical to those described in this chapter. Infants

were assigned to either surface cooling to 33.5°C or radiant warming to 36.5°C and 37.0°C. The intervention was commenced within 6 hours and continued for 72 hours, followed by at least 6 hours of active rewarming. Notably, 41 / 106 in the control group had a temperature > 38°C during the treatment period. Infants were evaluated at 18 to 22 months, the primary outcome measure of death or moderate-to-severe disability occurred in 44% of the hypothermia group and 62% of the control group (RR, 0.72; 95% CI 0.54 to 0.95, P = 0.01).<sup>2</sup>

The CoolCap trial randomised 234 infants  $\geq$  36 weeks gestation with moderate-to-severe HIE to standard care (maintenance of temperature at  $37.0 \pm 0.2^\circ\text{C}$ ) or mild systemic hypothermia (target rectal temperature  $34^\circ\text{C}$  to  $35^\circ\text{C}$ ) and the application of a cap which circulated water at  $8^\circ\text{C}$  to  $12^\circ\text{C}$ ). The intervention began within 6 hours of birth and was continued for 72 hours. The investigators hypothesised the intervention would have the greatest benefit for those with moderate encephalopathy. There was no difference in the primary outcome measure of death or severe disability at 18 months; 66% of the standard care group and 55% of the intervention group (OR, 0.61; 95% CI, 0.34 to 1.09; P = 0.1). However, after adjustment for baseline differences in EEG severity, this became statistically significant (OR, 0.57; 95% CI, 0.32 to 1.01; P = 0.05). *A priori* subgroup analysis demonstrated the majority of benefit was derived from the cohort of infants with least severe EEG changes (n= 172; OR, 0.42; 95% CI, 0.22 to 0.80; P = 0.009). The number needed to treat to avoid one death or child with severe disability was six.<sup>5</sup>

In further multivariate analysis of the CoolCap trial, cooling was a predictor of favourable outcome (OR, 0.52; 95% CI, 0.28 to 0.97; P = 0.04). Predictors of unfavourable outcome were grade 3 encephalopathy (OR, 3.37; 95% CI, 1.64 to 6.93; P = 0.001), a severely abnormal EEG (OR, 2.06; 95% CI, 1.01 to 4.17, P = 0.05), seizure activity on EEG (OR, 1.96; 95% CI, 1.02 to 3.74; P = 0.04) and increasing birth weight (in 100g steps) (OR, 1.06; 95% CI, 1.01 to 1.12; P = 0.03).<sup>11</sup>

For term births, the incidence of cerebral palsy in the US, Australia and Europe has remained largely static at approximately 2 per 1,000 live births over the last two decades.<sup>12</sup> A retrospective study used the Canadian cerebral palsy registry to determine how many cases of cerebral palsy could have been prevented by more widespread implementation of cooling for HIE. Of the 1,001 children registered over a 12 year period, only 64 met cooling criteria. The investigators predicted that 8 children over a 12 year period would have been spared neurological disability had cooling use been more widespread.<sup>13</sup>

## Should longer or deeper hypothermia be implemented for HIE?

No. It seems cooling to 33.5°C for 72 hours will remain standard practice.

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# Circulatory Trials



## ATHOS-3

**Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, et al. Angiotensin II for the Treatment of Vasodilatory Shock. N Engl J Med 2017;377:419-430**

### Introduction

Catecholamines have long been the principal choice of pharmacological vasoactive support for circulatory failure. However, this group of agents is not without problems. Dopamine, a precursor molecule for both adrenaline and noradrenaline, causes numerous unwanted effects, including immunosuppression, endocrine dysfunction and arrhythmias, and has fallen out of favour due to its unfavourable profile.<sup>1,2</sup> Adrenaline suffers from the induction of unwanted tachycardia and lactate production, clouding resuscitation attempts partly guided on serum lactate values.<sup>3</sup> Noradrenaline is likely the "cleanest" of the catecholamines, and provides much needed vasoconstriction, opposing the venodilation and reduction of stressed blood volume seen in sepsis.<sup>3</sup> Despite this, even noradrenaline has side effects, including digital and mesenteric ischaemia, myocardial injury and pulmonary hypertension.<sup>2</sup>

Due to the inherent limitations of catecholamine therapy, efforts at de-catecholising pharmacological support have gained momentum. Beta blockade, rather than beta agonism, has been successfully tested in the setting of sepsis,<sup>4</sup> with a further large scale UK trial currently in progress (ISRCTN12600919). Vasopressin, a peptide hormone produced in the hypothalamus and released from the posterior pituitary gland, has been examined as a vasopressor in the settings of cardiac arrest and sepsis. The recent VANISH trial, investigating vasopressin in sepsis, suggested a possible renoprotective effect in comparison with noradrenaline, but without a mortality benefit.<sup>5</sup> Levosimendan, a novel calcium sensitising inodilator, has also recently been investigated, not just in sepsis, but also in three major randomised controlled trials in the cardiac surgical setting. Unfortunately, levosimendan appeared to worsen organ dysfunction in the LeoPARDS sepsis trial,<sup>6</sup> and did not improve outcomes in any of the three cardiac surgical trials published this year (LEVO-CTS, LICORN and CHEETAH).<sup>6-8</sup>

It is in this setting that the third endogenous vasopressor system, after catecholamines and vasopressin, of renin-angiotensin-aldosterone has finally been subjected to a major randomised controlled trial. A major impediment to this line of research has been the inability to formulate angiotensin II with long term stability suitable for storage, which has now been overcome.

### Synopsis

ATHOS-3 was a phase 3, multi-centre, blinded, placebo-controlled, randomised trial

investigating angiotensin II for the treatment of vasodilatory shock requiring high-dose vasopressors. It was funded and sponsored by La Jolla Pharmaceutical Company, the manufacturers of synthetic human angiotensin II. In addition, the La Jolla Pharmaceutical Company helped design the trial, undertook the analysis, sat on the writing committee and funded a professional medical writer to assist with manuscript revisions during the publication submission. An independent data safety and monitoring committee provided oversight of the trial.

Patients were eligible if they were aged over 18 years, had vasodilatory shock after a minimum of 25 ml/kg IV fluid resuscitation and were receiving high dose vasopressors, defined as 0.2 µg/kg/min of noradrenaline or equivalent, for between 6 and 48 hours duration. Vasodilatory shock was defined as a mean arterial pressure (MAP) of between 55 and 70 mm Hg, with a cardiac index greater 2.3 L/min/m<sup>2</sup> or central venous oxygen saturation greater than 70%, and a central venous pressure greater than 8 mm Hg. There was a large number of exclusion criteria, including acute coronary syndrome, bronchospasm, liver failure, mesenteric ischaemia, haemorrhage, abdominal aortic aneurysm, venoarterial ECMO, neutropaenia (< 1000/mm<sup>3</sup>), high dose glucocorticoids and burns > 20% body surface area.

Block randomisation was performed in a 1:1 manner via a central web-based system, and was stratified for MAP (above or below 65 mm Hg) and APACHE II score (≤30, 31 to 40, ≥41). Both the angiotensin II and placebo solutions were prepared in identical saline bags. The research team, clinical staff, patients and families were unaware of treatment allocation.

The initial dose of the study drugs was equivalent to 20 ng/kg/min angiotensin II and was adjusted to achieve a MAP ≥ 75 mm Hg during the first three hours. Other vasopressors were held constant during this dose finding period unless absolutely necessary, which was deemed a non-response to the study drug. The maximum rate of angiotensin II was equivalent to 200 ng/kg/min. After 3 hours 15 minutes, all vasoactive agents, including the study drugs, could be adjusted to achieve a target MAP of 65 to 75 mm Hg. From this time point to 48 hours, the study drugs could be adjusted to angiotensin II equivalent doses of between 1.25 and 40 ng/kg/min. At 48 hours, the study drugs were tapered in a protocolised manner. If this was associated with an increase in the need for background vasoactive agents (noradrenaline equivalent rise > 0.1 µg/kg/min), or clinical instability, the study drugs could be recommenced for up to 7 days. If the study drug had been stopped for > 3 hours, it could not be reinstated.

The primary outcome was the MAP response at 3 hours, defined as a MAP of 75 mm Hg or higher or an increase in MAP ≥ 10 mm Hg from baseline, in the absence of an increase

of background vasoactive agents. Secondary outcomes were changes in the circulatory sequential organ failure assessment (SOFA) score and total SOFA score at 48 hours. Several safety outcomes were also recorded. Outcome measures were assessed in a hierarchical fashion.

300 patients were required to demonstrate a 20% absolute increase in the achievement of target blood pressure, from 40% in the placebo group to 60% in the angiotensin II group, with 90% power at a 5% significance level. One interim analysis was completed at the halfway point. The primary outcome was assessed with a modified intention-to-treat principle, with safety analyses restricted to those who received study drugs. Missing data was imputed from the last recorded value, except for safety data. Missing data, due to death, was considered as treatment failure.

ATHOS-3 was conducted from May 2015 to January 2017 in 75 ICUs in North America, Australasia and Europe. 404 patients were screened and 344 patients randomised. 23 randomised patients did not receive the study drug, most due to an improvement in their clinical condition. 163 patients received angiotensin II and 158 patients received placebo. Groups were well matched at baseline, with a typical patient being a 64 year old male North American, with a baseline median (IQR) MAP of 66 (63 - 69) mm Hg, an APACHE II score of 28, an ScvO<sub>2</sub> of 77%, and a cardiac index of 3.1 L/min/m<sup>2</sup>. Approximately 80% of patients were septic, and 16% had been exposed to either an ACE inhibitor or angiotensin-receptor blocker, values which were similar between groups. Vasopressor dose were also similar at baseline, being approximately 0.33 µg/kg/min noradrenaline equivalents. Almost all patients were receiving noradrenaline at baseline, with approximately 70% of both groups also receiving vasopressin in the 6 hours prior to commencement of study drugs. Data was available for all participants.

The full 48 hour infusion was completed in 86% of the angiotensin II group and 78.5% of the placebo group, indicating excellent exposure to the experimental therapy. For the primary outcome, patients in the angiotensin II group had a significantly better response to angiotensin II than placebo, achieving the target MAP of 75 mm Hg or higher, or an increase in MAP  $\geq 10$  mm Hg from baseline (69.9% vs. 23.4%; OR, 7.95; 95% CI, 4.76 to 13.3; P < 0.001). Angiotensin II administration also resulted in a significant increase in MAP over the initial 3 hour period (12.5 mm Hg vs. 2.9 mm Hg; P < 0.001). Both the study drug dose and background vasopressor doses were lower in the angiotensin II group than in placebo. For the secondary outcomes of change in circulatory SOFA score at 48 hours, angiotensin II showed an improvement over placebo ( $-1.75 \pm 1.77$  vs.  $-1.28 \pm 1.65$ ; P = 0.01), although there was no difference in total SOFA score at this time point ( $1.05 \pm 5.50$  vs.  $1.04 \pm 5.34$ ; P = 0.49). There was no difference in mortality at day 7 (angiotensin



II vs. placebo; 28.8% vs. 34.8%; HR, 0.78; 95% CI, 0.53 to 1.16; P = 0.22) or day 28 (46.0% vs. 53.8%; HR, 0.78; 95% CI, 0.57 to 1.07; P = 0.12).

Other interesting results included a larger decrease in mean noradrenaline-equivalent dose ( $-0.03 \pm 0.10$  vs.  $0.03 \pm 0.23$ ,  $P < 0.001$ ) and a greater MAP response with angiotensin II in those receiving lower dose noradrenaline equivalents of  $0.5 \mu\text{g}/\text{kg}/\text{min}$  ( $n = 91/117$  vs.  $23/46$ ; 77.8% vs. 50%;  $P < 0.001$ ). There was no signal of harm from any of the reported safety analyses: (angiotensin II vs. placebo) adverse events of any grade, 87.1 vs. 91.8%; serious adverse events, 60.7% vs. 67.1%; and rates of infusion discontinuation, 14.1% vs. 21.5%. The heart rate was consistently higher in the angiotensin group.

## Critique

ATHOS-3 appears to be a breakthrough trial in the long struggle for an alternative to catecholamines in the management of shock. The methodology appears sound, the trial conduct intact and the results coherent. On the surface, all appears well. Delving deeper into the study, however, a number of issues arise.

The trial looks to have high internal validity; i.e. it did what it said it was going to do. The population recruited was very sick, as demonstrated by the relatively high vasopressor requirement, high median APACHE II scores and high mortality. The groups were similar at baseline and were randomised appropriately. However, 7% ( $n = 23$ ) of the randomised population did not receive the study drug. While these patients were excluded from the modified intention-to-treat analysis, which was used for the primary outcome analysis, reassuringly the sensitivity intention-to-treat analysis produced a similar result.

As expected for a study of vasodilatory shock, the majority of patients had septic shock (approximately 80%). Therefore, ATHOS-3 could almost be considered a sepsis trial, with a resultant focus on the major confounders of time to anti-microbial therapy and source control, appropriateness of these interventions, pathogens, source of infection and fluid resuscitation. Randomisation should balance these factors out, but it is possible it may not. Unfortunately these data were not recorded. The two groups did, however, have near identical median  $\text{ScvO}_2$  at 77%, and thus may have been reasonably well, and equally, resuscitated at baseline.

Syndromic trials unfortunately frequently recruit very heterogenous groups, minimising the potential to identify a signal of benefit. As a trial investigating a vasopressor for the syndrome of vasodilatory shock, it is somewhat reassuring to see efforts were made to accurately identifying a population genuinely with this condition. A clear definition was employed and invasive monitoring used to obtain objective cardiac performance

measurements in almost 50% of patients. Unfortunately this also leaves 50% without solid evidence of vasodilatory shock, as the remaining indices used are limited - central venous pressure is known to be a poor predictor of volaemic status and ScvO<sub>2</sub> is a complex parameter affected by more than just vasodilation. For those with measurements, at approximately 3.1 L/min/m<sup>2</sup>, the cardiac indexes were consistent with this diagnosis. Similarly, other confounders such as anti-hypertensives, and specifically angiotensin-2 receptor blockers and angiotensin-converting enzyme inhibitors, were equally balanced between the two groups. The use of vasopressin within the 6 hours prior to randomisation was high at ~ 70% in both groups, and comparable doses of vasopressors were administered. It is mildly disappointing that levels of fluid administration prior to randomisation were not reported, although in subsequent correspondence it was revealed that patients in the angiotensin II group received less fluid volume during the initial 3-hour titration phase than patients in the placebo group (median volume, 447 ml vs. 602 ml; P < 0.001).<sup>9</sup>

The delivery of the intervention appears sound and has a clear rationale. By initially maintaining a constant dose of the background vasopressors, the effect of the study drugs could be ascertained. In the second part of the administration schedule, all agents could be varied as per the treating clinical team, mimicking reality, with the aim of first reducing vasopressin, should it be running, followed by catecholamines, and lastly angiotensin II, which should have been weaned off by 48 hrs. In both phases, the angiotensin II administration resulted in at least equal blood pressures at lower catecholamine levels.

This brings the next topic into focus – the choice of end-point. As a phase III trial, it would have been preferable to have patient-centred outcomes, especially for the primary endpoint. As a vasopressor seeking to achieve a blood pressure response, it appears the US Food and Drug Administration (FDA) mandated this primary outcome.<sup>10</sup> This is somewhat offset by the non-statistically significant, but consistent, parity or better results with angiotensin II. It is clear from this small trial that angiotensin II increases blood pressure. What this small trial is unable to definitely demonstrate is both safety, due to its size, and clinical benefit, as it was not powered for mortality, nor included either functional assessments or long term outcomes. Despite this, ATHOS III is a very valuable next step along the road to determining the clinical efficacy of angiotensin II.

The continued use of non-patient centred outcomes is a difficult issue. The ATHOS III investigators themselves warn of not heeding history. The nitric oxide synthase inhibitor 546C88 was similarly reported to improve blood pressure and reverse shock in an international randomised controlled trial in 312 patients with septic shock in 2004.<sup>11</sup>

Patient centred outcomes were listed as secondary endpoints and did not differ between groups. A subsequent, larger randomised controlled trial (n = 797) was halted on safety grounds after an interim analysis showed increased mortality with the experimental therapy at 28 days (59% vs. 49%; P < 0.001).<sup>12</sup> This was largely due to circulatory effects from the nitric oxide synthase inhibitor.

It is for many of these reasons that it was surprising (although this was predicted)<sup>10</sup> to see the FDA licence angiotensin II (Giapreza) for use in “septic and other vasodilatory shock” on December 21<sup>st</sup>.<sup>13</sup> The application by the La Jolla Pharmaceutical Company, the makers of angiotensin II, received a “Priority Review” by the FDA, which occurs when *“the agency determines that the drug, if approved, would significantly improve the safety or effectiveness of treating, diagnosing or preventing a serious condition”*. This may reflect a lower level of regulation favoured by the Trump administration, making it easier for pharmaceutical compounds to reach the general market. However, it has been anticipated the Australian regulator would follow suit.<sup>10</sup>

It will be interesting to see if clinicians in the USA start using angiotensin II in the absence of adequately powered patient-centred outcomes. Presumably phase 4 surveillance will occur, which will equally make for interesting reading, given the manner in which angiotensin II was used in this trial. With an initial 3 hour titration using higher doses, followed by a decrease to lower doses, thus reducing the potential for harm. Will clinicians use angiotensin II in the same manner, or will they be more likely to maintain it at the higher rate, content that surrogate measures, such as blood pressure, are adequately maintained. If the regulator is satisfied with surrogate measures, why not clinicians?

A small aside to the FDA release was the disclosure that the angiotensin group suffered more thromboembolic phenomenon (12.9% vs 5%), although this appears to be predominantly due to mild or moderate reactions, rather than severe, life-threatening or fatal reactions (personal communication with chief investigator, Dr Ashish Khanna).

On a similar note, it is now unusual to see such level of industry involvement in a clinical trial. La Jolla instigated, funded and sponsored ATHOS III, as well as being involved in the trial design, analysis, and manuscript preparation. They also paid for a professional medical writer to assist with the manuscript revisions. It has been well described that trials with significant industry engagement are more likely to report statistically significant results than those lacking such ties.

This returns the critique back to question of efficacy. While ATHOS III clearly demonstrated a restorative effect on blood pressure, it is intriguing to see the

circulatory component of the SOFA score improve at 48 hours, while the combined SOFA score remained unchanged, implying a different SOFA component worsened.

This study is really about two issues; firstly, would the novel angiotensin II preparation be adequate for clinical use and secondly, would angiotensin II increase blood pressure in critically ill patients with vasodilatory shock. This is what the study sets out to achieve, and it does so. Patient centred-outcomes, the aspect clinicians are interested in, are of secondary importance. In itself, this is not an issue, as the next larger study should address these more formally.

In summary, ATHOS III demonstrates both a restorative blood pressure effect in critically ill patients with vasodilatory shock and the adequacy of the novel drug preparation. This small trial, however, is underpowered for patient centred outcomes and is too small to adequately assess safety. It is, however, a welcome step forward in the pursuit of another vasopressor. Now it is time for the next step.

### **Where this sits in the body of evidence**

As this is the first phase III randomised controlled trial of angiotensin II in vasodilatory shock, the evidence-base is presently limited to a single pilot trial. Two other approaches have been taken to de catecholamine patients in septic shock, vasopressin and beta blockade.

The ATHOS trial was a pilot study seeking to determine the effect of angiotensin II on the dose of noradrenaline required to maintain a MAP of 65 mm Hg in 20 patients with high output shock.<sup>14</sup> Patients were randomised to either a 6 hour infusion of angiotensin II or placebo. Angiotensin II was effective in reducing mean 1-hour noradrenaline requirements ( $7.4 \pm 12.4$  mcg/min vs.  $27.6 \pm 29.3$  mcg/min), with a dosing range of approximately 2 - 10 ng/kg/min. There were no differences in patient centred outcomes, although the pilot trial was not powered for these.

The VANISH trial investigated whether 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.<sup>5</sup> In a 2x2 factorial design, 421 patients were randomised to either vasopressin and placebo, vasopressin and steroids, noradrenaline and placebo or noradrenaline and steroids. 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. Only once vasopressin or noradrenaline infusions were at maximal doses was the second drug added (i.e. hydrocortisone 50 mg 6 hourly or placebo). There was no difference in the primary outcome, 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). No effect was seen from steroids.

In an attempt to lessen the deleterious effects of beta agonism in septic shock, Morelli and colleagues completed a single centre, open-label, randomised controlled trial, investigating esmolol in 154 tachycardiac (heart rate > 95/min), septic patients requiring noradrenaline to maintain a MAP of 65 mm Hg.<sup>4</sup> Esmolol was effective reducing heart rate, improving mechanical cardiac performance, reducing the requirement for noradrenaline and fluid and improving mortality at 28 days (49.4% vs. 80.5%; adjusted hazard ratio, 0.39; 95% CI, 0.26 to 0.59; P < 0.001). The trial was limited by the very high mortality in the control group and the high use of rescue levosimendan (approximately 45%).

The multi-centre, double-blind, VASST trial randomised 778 patients with septic shock requiring at least 5 µg/min of noradrenaline to either low-dose vasopressin (0.01 to 0.03 U/min) or norepinephrine (5 to 15 µg/min) in addition to open-label vasopressors.<sup>15</sup>

There were no significant differences in the 28-day mortality rate (vasopressin vs. norepinephrine groups, respectively; 35.4% vs. 39.3%, P = 0.26), 90-day mortality (43.9% vs. 49.6%; P = 0.11) or rates of serious adverse events (10.3% vs. 10.5%; P = 1.00). Of note, in an *a priori* analysis, the mortality rate was lower in those with less severe septic shock treated with vasopressin (26.5% vs. 35.7%, P = 0.05).

### **Should we begin using angiotensin II for vasodilatory shock?**

No. Although ATHOS-3 establishes pharmacodynamic effects, and pharmacological suitability for use, a larger multi-centre trial with patient-centred outcomes is required to establish efficacy and safety.

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## CULPRIT-SHOCK

**Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, et al. PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock. N Engl J Med 2017;377:2419-2432**

### **Introduction**

It is widely accepted that early revascularization, either with coronary artery bypass grafting (CABG) or primary percutaneous coronary intervention (PCI), should be performed in patients with ST-segment elevation myocardial infarction (STEMI).<sup>1</sup> Long term follow up from the SHOCK trial reported that early revascularization saves lives, with a number needed to treat of eight.<sup>2,3</sup> Having established that early revascularization is beneficial, investigators have attempted to answer the question whether all stenotic arteries should be treated with PCI in the setting of acute myocardial infarction (AMI). The PRAMI trial demonstrated that multivessel PCI reduced the composite outcome of cardiac mortality, nonfatal myocardial infarction, or refractory angina in comparison to culprit-lesion-only PCI.<sup>4</sup> However, patients with cardiogenic shock were specifically excluded.

Cardiogenic shock develops in 5 to 15% of patients with AMI, translating to 60,000 to 70,000 cases each year across Europe.<sup>3</sup> Controversy exists as to whether patients with cardiogenic shock following AMI should undergo multivessel PCI or culprit-lesion-only PCI. It would seem intuitive that complete revascularization using multivessel PCI would improve myocardial blood flow and cardiogenic shock. However, the higher volume of contrast required to achieve complete revascularization may worsen pulmonary oedema, increase end diastolic volume and transmural pressure causing a reduction in myocardial blood flow, or worsen renal injury. As a result, a trial examining the role of multivessel PCI compared to culprit-lesion-only PCI in patients with AMI and cardiogenic shock was warranted.

### **Synopsis**

CULPRIT-SHOCK was a multicentre, open-label, randomised controlled trial which hypothesised that in patients with cardiogenic shock due to AMI, immediate revascularization of only the culprit-lesion would improve outcomes in comparison to immediate multivessel PCI. Patients with cardiogenic shock (Table 2) due to AMI and multivessel disease were eligible. Multivessel disease was defined as > 70% stenosis of two or more major vessels (a major vessel being defined as a diameter  $\geq$  2 mm). Patients with either STEMI or non ST-segment elevation myocardial infarctions (NSTEMI) were included. There was an extensive list of exclusion criteria, including: need for urgent



coronary artery bypass grafting, cardiopulmonary resuscitation > 30 minutes, alternative cause of shock, creatinine clearance < 30 mL/min and life expectancy < 6 months.

Cardiogenic Shock
Systolic blood pressure < 90 mm Hg for > 30 minutes
Catecholamines required to achieve a systolic blood pressure > 90 mm Hg
Pulmonary oedema
Evidence of impaired organ perfusion (cold and clammy limbs, lactate > 2 mmol/L, urine output < 30 ml/hr or altered mentation)

**Table 2. Definition of cardiogenic shock**

Patients were recruited within 12 hours of onset of shock and randomised in a 1:1 manner to one of two treatment strategies; PCI to the culprit-lesion-only (with optional revascularization of the non-culprit lesions at a later date) or immediate multivessel PCI of all major vessels with stenosis > 70% diameter. Randomisation was performed immediately after diagnostic angiography and was stratified based on centre. The use of mechanical support was at the discretion of the treating centre.

The primary outcome measure was a composite of all cause 30-day mortality or renal failure requiring renal replacement therapy (RRT) within the first 30 days. RRT was initiated for circulatory overload refractory to medical therapy, potassium > 6.0 mmol/L refractory to medical therapy, urea > 50 mg/dL (> 8.4 mmol/L) or pH < 7.2. Among the 19 secondary endpoints were separate measures of all cause 30-day mortality, need for RRT, further AMI, cardiac failure requiring rehospitalisation, need for repeat revascularization, time to haemodynamic stability, need for catecholamines, ICU length of stay, and need for mechanical ventilation. Safety outcome measures were bleeding and stroke.

The investigators assumed the primary outcome measure would occur in 50% of the multivessel PCI group and 38% of the culprit-lesion-only group. On this basis, 684 patients were required to achieve an 80% power with a two-sided alpha level of 0.048 (adjusted to account for one interim analysis performed after recruitment and 30 day follow up of half the patients). A target of 706 patients was set to allow for withdrawals. Analysis was performed on an intention-to-treat basis, with sensitivity analyses also undertaken. Multiple subgroup analyses were included; age, sex, anterior vs. non-anterior AMI, STEMI vs. NSTEMI, two vs. three vessels affected, and the presence of a number of co-morbidities.

Over a four year period across 83 European centres, 1,075 patients were screened, 706 were recruited and data was available for 686 patients; 344 and 342 in the culprit-lesion only and multivessel PCI groups, respectively. Approximately half the exclusions (184 / 369) were because the patient had single vessel coronary artery disease only. The two groups were well balanced at baseline with a typical patient being a 70 year old male with a history of at least one risk factor for ischaemic heart disease. Approximately one in six had a previous AMI. Renal function was also similar between the two groups. The median systolic blood pressure was 100 mm Hg in both groups and evidence of impaired organ perfusion was common; cold & clammy limbs (69.7%), altered mentation (67.6%), lactate > 2 mmol/L (66.3%) or urine output < 30 mL/h (26.2%). In total, 62.4% of patients had suffered a STEMI, approximately half of which were anterior STEMIs. A further 14.8% of patients had left bundle branch block (LBBB). The majority of patients (63.4%) had three affected major vessels. The median (IQR) ejection fraction was 33% (25 to 40%) and 30% (21 to 40%) in the culprit-lesion-only and multivessel PCI groups respectively. The most common sites for the culprit lesion were left anterior descending artery (42.0%), right coronary artery (27.9%), left circumflex artery (21.3%) and left main stem artery (7.8%).

The interventions in the two groups were largely similar. Femoral arterial access was the commonest access route (82.3%), with 89.5% of patients receiving a drug eluting stent to the culprit lesion. The distribution of Thrombolysis in Myocardial Infarction (TIMI) grades for blood flow in the culprit lesion vessel prior to PCI were similar in the two groups (just over half had no flow). After PCI to the culprit lesion vessel, 84.5% and 86.7% of the culprit-lesion-only and multivessel PCI groups, respectively, had normal blood flow. There was clear separation between the two groups with regard to immediate complete revascularization, with 81% of the multivessel PCI group achieving this compared with just 7.6% of the culprit-lesion-only group ( $P < 0.001$ ). However, there was appreciable cross over between the two groups with 12.5% of the culprit-lesion-only group receiving multivessel PCI and 9.4% of the multivessel PCI group undergoing PCI solely to the culprit lesion. A further 17.7% of the culprit-lesion-only group underwent subsequent revascularization. Approximately one in four patients received some form of mechanical support during revascularization, which was similar between the two groups. The use of antiplatelets and anticoagulants was also similar between the two groups. The multivessel PCI group received more contrast material (median/IQR); 250 (200 to 350) vs. 190 (140 to 250) ml;  $P < 0.001$ .

The primary end point of all-cause mortality or need for RRT by day 30 had occurred in 45.9% of the culprit-lesion-only PCI group compared to 55.4% of the multivessel PCI group (relative risk (RR), 0.83; 95% CI, 0.71 to 0.96;  $P = 0.01$ ). The results were unchanged in the per protocol and as treated analyses. The results were consistent across all pre-

specified subgroups with all point estimates favouring the culprit-lesion-only group except patients aged < 50 years {however, there were only 33 patients in this group and the estimate is imprecise with a wide confidence interval (RR, 1.88; 95% CI, 0.56 to 6.29)}.

Among the secondary end points, death was less common in the culprit-lesion-only PCI group (43.3%) than the multivessel PCI group (51.6%) (RR, 0.84; 95% CI, 0.72 to 0.98; P = 0.03). There was no significant difference in the need for RRT; culprit-lesion-only PCI group, 11.6% vs. multivessel PCI group, 16.4% (RR, 0.71; 95% CI, 0.49 to 1.03; P = 0.07). There was a significant decrease in eGFR on days 3 and 4 in the multivessel PCI group (both P = 0.04). There was no difference in the need for catecholamine therapy (approximately 90% in both groups), duration of catecholamine therapy (3 days) or rates of recurrent AMI, rehospitalisation for congestive heart failure, stroke or bleeding between the two groups. No adjustment made for multiple testing.

## Critique

This excellent open-label, randomised, controlled trial examined the role of PCI in patients with multivessel coronary artery disease and cardiogenic shock in the setting of an AMI. This trial had many strengths. There were clear definitions for cardiogenic shock, patient outcomes and safety outcomes. As the patients, their coronary blood flows, and use of medical and mechanical support (which was high) was described in immense detail, it is easy to picture the type of patient this trial result is applicable to. Recruiting 706 patients in this very specific and acutely unwell group is noteworthy. To achieve this required recruitment from 83 centres over four years. The screened to enrolled ratio was high, with 65.7% of those screened enrolled. Unfortunately, due to an administrative oversight, 13 patients had been enrolled at Heart Centre Leipzig University Hospital prior to the trial being registered at clinicaltrials.gov.

This is one of the largest studies to date examining the role of either immediate versus deferred revascularization or culprit-lesion-only PCI versus multivessel PCI.<sup>1,2,4-6</sup> In including a cohort of patients with cardiogenic shock it studied a population different than previous trials of culprit-lesion-only PCI versus multivessel PCI.<sup>4-6</sup> This may explain why the observed mortality was considerably higher than the 2-6% seen in previous trials which recruited patients with multivessel disease but without cardiogenic shock.<sup>4-6</sup> CULPRIT-SHOCK also included patients with chronic total occlusion of arteries which means revascularization is technically challenging and confers a higher risk of complications.<sup>7</sup> Mortality was comparable to the 56 to 66% in-hospital mortality observed in the registry of patients with cardiogenic shock and AMI collected at the time of the original SHOCK trial.<sup>1</sup> Given the higher risk population, it is unclear why a composite outcome measure of mortality or need for RRT at 30 days, as opposed to

mortality alone, was chosen. The two components of this composite outcome measure are not of equal importance to patients. In examining a cohort with such a high mortality, it may have been possible to power a trial with mortality as a primary outcome measure. Previous studies examining the role of PCI have investigated lower risk populations with a low event rate. This has necessitated the use of MACE (Major Adverse Cardiac Events, namely all-cause mortality, recurrent myocardial infarction, heart failure, and the need for revascularization due to ischaemia) outcomes to achieve power.<sup>5</sup>

The results of this trial are at odds with the current body of evidence where multivessel PCI at the time of initial presentation has consistently been shown to reduce mortality and the need for subsequent revascularization procedures in a population with AMI without shock.<sup>4,5</sup> In the CULPRIT-SHOCK trial, the point estimates for the intention-to-treat analysis, per protocol analysis, as-treated population analysis, and pre-specified subgroup analysis, consistently showed a benefit with culprit-lesion-only PCI. The sole exception to this was the subgroup of patients ages < 50 years (although there were only 33 patients in this group and the estimate is imprecise with wide confidence intervals). The coherency in results across multiple analyses provides reassurance about the robustness of the result, despite it being contrary to the current body of evidence. There is a notable caveat - in the CULPRIT-SHOCK trial the end point was 30-day mortality. The Kaplan-Meier curves for MACE outcomes in the PRAMI and CvLPRIT trials continue to separate for up to three years after PCI in favour of the multivessel PCI group,<sup>4,5</sup> possibly derived from a reduction in the need for subsequent revascularization. In both the PRAMI and CvLPRIT trials, multivessel PCI resulted in a reduction in mortality by approximately two thirds, although due to the low event rate in these lower risk populations these findings did not reach statistical significance. When considering where CULPRIT-SHOCK sits in the body of evidence, this trend is hard to ignore completely. Moreover, long term follow up of patients from the SHOCK trial demonstrated that the full mortality benefits from PCI took six years to develop.<sup>2</sup> The question is, was the follow up period in the CULPRIT-SHOCK trial long enough to delineate the true benefit or harm from culprit-lesion-only PCI?

There was reasonable crossover between the two groups (12.5% of the culprit-lesion-only group received multivessel PCI and 9.4% of the multivessel PCI group underwent culprit-lesion-only PCI). In the culprit-lesion-only group, 12 patients received multivessel PCI due to cardiovascular deterioration or failure of resolution of shock, a further seven for operator preference. This may be indicative of a lack of equipoise in some cases. An alternative explanation is that CULPRIT-SHOCK, unlike PRAMI which only enrolled STEMI patients, enrolled patients with NSTEMI or LBBB, therefore making it harder to identify the culprit infarct territory.<sup>4</sup> In many cases failure to undergo multivessel PCI as planned was as a result of technical difficulties, perceived futility or death.

In this trial, how culprit-lesion-only PCI benefits patients (or indeed how multivessel PCI harms them) is unclear. The investigators postulated initially that the increased contrast load may be implicated in renal injury. However, the need for RRT was similar in both groups. There was a small, but statistically significant, reduction in the eGFR seen in the multivessel PCI group in days three and four but as no correction was made for multiple testing this must be considered an exploratory finding. Overall, there were 27 extra deaths in the multivessel PCI group. The biggest cause of this was an additional 14 deaths from neurological causes, a further 10 deaths were classified as “unknown” or “other”. So, an alternative explanation must be sought. It may be that shocked patients need a period of physiological stability prior to definitive multivessel revascularization (analogous to using damage control surgery and damage control resuscitation in trauma).<sup>8,9</sup> In previous trials, patients were scheduled to undergo multivessel revascularization prior to hospital discharge but not necessarily at the time of primary PCI - splitting this may have reduced the physiological burden and prevented further events.<sup>5</sup>

Overall when examined in isolation this was an excellent trial. However, it goes against the current body of evidence, the investigators are unable to provide a strong biological rationale for the excess mortality in multivessel PCI group and the long term outcomes of a culprit-lesion PCI strategy are unknown. As such, further work is needed to determine the risks and benefits from a culprit-lesion-only PCI strategy in patients with cardiogenic shock in AMI.

### **Where this sits in the body of evidence**

The SHOCK trial examined the role of early revascularization in patients with AMI and cardiogenic shock. Patients with STEMI, new LBBB or a Q-wave infarctions were included. 302 patients from 30 sites were randomised to undergo revascularization with either PCI or CABG within six hours of presentation or medical management including thrombolysis. In the medical management group, PCI was permitted after 54 hours post randomisation. In the revascularization group, 64% had PCI, the remaining 36% underwent urgent CABG. There was no difference in the primary end point of 30-day mortality; 46.7% in the revascularization and 56.0% in the medical management groups (difference, -9.3%; 95% CI, -20.5 to 1.9%; P = 0.11). However six-month mortality was lower with revascularization (50.3%) than medical-therapy (63.1%, P = 0.027).<sup>1</sup>

Follow up of patients from the SHOCK trial demonstrated the longer term survival benefit from early revascularization, with 32.8% of the early revascularization group and 19.6% of the medical management group being alive at 6 years. Of those who survived to hospital discharge, benefits continued to be observed, with a lower mortality seen in the early revascularization group (HR, 0.59; 95% CI, 0.36 to 0.95; P = 0.03).<sup>2</sup>

Multivariate analysis of the SHOCK trial using a Cox proportional hazards regression model demonstrated that the main independent risk factors for survival at one year included higher TIMI flow grade (HR for death, 0.85 per 1 grade increase; 95% CI, 0.73 to 0.99; P = 0.032) and culprit vessel (right coronary vs. left anterior descending, HR for death, 0.41; 95% CI, 0.32 to 0.52; P = 0.004). A higher number of affected arteries was only associated with an increase in mortality in the patient cohort who were managed medically.<sup>10</sup>

The PRAMI trial compared culprit-lesion-only PCI to multivessel PCI in a cohort of 465 patients with AMI due to STEMI in the absence of shock. Patients were required to have multivessel coronary disease with  $\geq 50\%$  stenosis on angiography. Patients with chronic total occlusion of vessels or an indication for urgent coronary artery bypass grafting were excluded. The primary endpoint was a combination of death from cardiac causes, non-fatal AMI, or refractory angina. The trial was terminated early due to a highly significant result at interim analysis in favour of multivessel PCI. The primary outcome measure occurred in 9% of the multivessel PCI group compared to 23% of the culprit-lesion-only group (HR, 0.35; 95% CI, 0.21 to 0.58; P < 0.001). The benefit was largely derived from a reduction in non-fatal AMI and refractory angina. The reduced rate of death from cardiac causes did not reach statistical significance (HR, 0.34; 95% CI, 0.11 to 1.08; P = 0.07). Caution should be exercised in interpreting these results due to the low number of events in each group.<sup>4</sup>

In 2015, the CvLPRIT trial randomised 296 patients with STEMI to culprit-lesion-only PCI or complete revascularization either during primary PCI or prior to hospital discharge. The primary composite endpoint was assessed at one year and consisted of mortality, recurrent AMI, heart failure, or need for revascularization. The primary endpoint occurred less commonly in the complete revascularization group than the culprit-lesion-only group; 10.0% vs. 21.2% (HR, 0.45; 95% CI, 0.24 to 0.84; P = 0.009). There was no statistical difference in any of the individual components in the primary outcome measure.<sup>5</sup>

The DANAMI-3-PRIMULTI trial randomised 627 patients with STEMI to either culprit-lesion-only PCI or complete revascularization. Fractional flow reserve modelling was used to determine which vessels required intervention in the complete revascularization group. The primary outcome was incidence of MACE at follow-up of a minimum of one year. After a median follow up of 27 months there was a significant reduction in primary outcome measure seen in the complete revascularization group (13%) compared to the culprit-lesion-only group (22%) (HR, 0.56; 95% CI, 0.38 to 0.83; P = 0.004). The majority of benefit was derived from a reduction in the need for subsequent urgent and non-urgent PCI in the complete revascularization group.<sup>6</sup>

The multicentre, open-label, randomised, controlled IABP-SHOCK-II trial investigated the use of intra-aortic balloon pump in 600 patients with cardiogenic shock undergoing early revascularization (575 patients underwent primary PCI). Patients were randomised to IABP or medical therapy. There was no significant difference in the primary outcome measure of 30 day mortality, or outcomes at 12 month follow up including: mortality, 52% vs. 51% in the IABP and control groups, respectively (RR, 1.01; 95% CI, 0.86 to 1.18; P = 0.91) reinfarction, 9% vs. 3% (RR, 2.60; 95% CI, 0.95 to 7.10, P = 0.05), need for recurrent revascularization, 20% vs. 22% (RR, 0.91; 95% CI, 0.58 to 1.41; P = 0.77), or stroke, 2% vs. 1% (RR, 1.50, 95% CI, 0.25 to 8.84, P = 1.00).<sup>11</sup>

### **Should we routinely provide culprit-lesion-only PCI in the setting of AMI-associated cardiogenic shock?**

Maybe. Further research is warranted.

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## CHEETAH

**Landoni, G, Lomivorotov V, Alvaro G, Lobreglio R, Pisano A, Guarracinoet F et al. Levosimendan for Hemodynamic Support after Cardiac Surgery. N Engl J Med 2017; 376(21):2021-2031**

### Introduction

Despite the increasing use of percutaneous interventions, cardiac surgery remains a common intervention in patients with heart disease.<sup>1</sup> The risk of cardiac surgery has declined but increasingly older patients with associated comorbidities are referred for intervention.<sup>2</sup> For these patients, the peri-operative risk of complications and death is potentially much higher. One such major complication is acute perioperative myocardial dysfunction, commonly referred to as low cardiac output syndrome. This syndrome manifests as a variable degree of systolic and diastolic ventricular dysfunction, leading to reduced cardiac output and tissue hypoxia.<sup>3</sup> Low cardiac output syndrome is associated with an increase in morbidity and mortality, prolongation of intensive care stay and increased health care costs.<sup>3</sup> Treatment remains supportive with inotropes, vasopressors and mechanical assist devices.<sup>4</sup>

Levosimendan is a calcium sensitizing inotropic drug with vasodilator properties which may be superior to traditional inotropes in patients with heart failure.<sup>5</sup> In contrast to catecholamines, levosimendan causes increased myocardial contraction with a reported minimal increase in myocardial energy demand.<sup>6</sup> Furthermore, levosimendan causes coronary artery vasodilation potentially improving perfusion of ischaemic myocardium.<sup>7</sup> Levosimendan would therefore seem an ideal agent to treat low cardiac output syndrome. However, two trials<sup>8,9</sup> published this year have failed to show a major clinical benefit of prophylactic levosimendan in a selected higher risk group of cardiac surgery patients. In contrast, the CHEETAH trial used levosimendan as a treatment once low cardiac output syndrome had developed.

### Synopsis

This was a multicentre, randomised trial performed in 14 cardiac surgery units in Italy, Russia and Brazil. The primary aim was to investigate the effect of a levosimendan infusion, in addition to standard therapy, on mortality in patients with post cardiac surgery myocardial dysfunction.

Adult patients scheduled for cardiac surgery who had perioperative cardiovascular dysfunction, such as preoperative ejection fraction <25%, or patients who developed perioperative myocardial dysfunction, were eligible for enrolment. Myocardial dysfunction was defined as either a requirement for preoperative intra-aortic balloon

pump (IABP) or the need for an IABP or high dose inotropes within 24 hours of surgery. High-dose inotropic support was defined as a vasoactive-inotropic score >10, where the score was calculated as follows: dobutamine dose (in  $\mu\text{g}/\text{kg}/\text{min}$ ) + dopamine dose (in  $\mu\text{g}/\text{kg}/\text{min}$ ) + enoximone dose (in  $\mu\text{g}/\text{kg}/\text{min}$ ) + [adrenaline dose (in  $\mu\text{g}/\text{kg}/\text{min}$ ) x 100] + [noradrenaline dose (in  $\mu\text{g}/\text{kg}/\text{min}$ ) x 100]. Patients were excluded if they had a previous adverse reaction to levosimendan, or had received levosimendan in the month prior to surgery, had a liver or renal transplant, liver cirrhosis, were not for resuscitation or a decision to use extracorporeal oxygenation had been made.

Eligible patients were randomised using a computer generated sealed envelope procedure, with stratification according to trial centre, to receive levosimendan or placebo infusion. The infusion was commenced at a dose of 0.05  $\mu\text{g}/\text{kg}/\text{min}$  and titrated at the discretion of the attending physician for a maximum of 48 hours. The infusion was titrated between 0.025  $\mu\text{g}/\text{kg}/\text{min}$  to 0.2  $\mu\text{g}/\text{kg}/\text{min}$ . A flowchart was provided for inotrope management but was not mandatory. All subsequent clinical management was decided by the attending physician.

The primary outcome was 30-day mortality. Secondary endpoints included acute kidney injury (as per RIFLE criteria), need for renal replacement therapy (RRT), duration of mechanical ventilation, ICU and hospital stay and a composite of death and RRT. Data was also collected on mechanical circulatory support, myocardial infarction, neurological morbidity, sepsis, pneumonia and mediastinitis and requirement for tracheostomy.

Assuming an estimated mortality rate of 10% in the placebo group, a total sample size of 870 patients was calculated to give 80% power to detect a 50% relative reduction in mortality in the levosimendan group, with a two-sided alpha error of 0.05

Over 6.5 years, a total of 4,725 patients were consented preoperatively; 647 met inclusion criteria with 506 patients randomised, 248 to levosimendan and 258 to placebo. The majority of patients were randomised in theatre (61 patients) or the intensive care unit (329 patients) because of high dose inotropes. Only 22 patients were randomised due to low ejection fraction, with the remaining patients requiring a IABP. Around 80% of patients were randomised in theatre or within 8 hours of arrival in the intensive care unit. Baseline characteristics were similar; patients were approximately 66 years old, mainly male (65%), 39% had a previous MI, 22% were diabetic and 30% had atrial fibrillation. About 60% of patients were either NYHA class III or IV, while most patients (76%) had an ejection fraction >40%.

Cardiopulmonary bypass was used in 98% of procedures. The surgery performed was diverse, with only 23% having isolated coronary artery bypass grafting (CABG). A further 29% had either mitral or aortic valve surgery in isolation or in combination with CABG.

The remaining operations incorporated a large range of procedures, including aortic surgery. Cardiopulmonary bypass times were approximately two hours.

Of the 506 patients randomised, there were only 15 protocol violations in each group, mainly interruption of the infusion. The infusion was administered for mean of  $33 \pm 14.6$  hours in the levosimendan group versus  $32 \pm 13.5$  hours in the placebo group. The mean dose was lower in the levosimendan group  $0.066 \pm 0.031 \mu\text{g/kg/min}$  versus an equivalent of  $0.075 \pm 0.033 \mu\text{g/kg/min}$  in the placebo group ( $P = 0.002$ ). Haemodynamic data was available for approximately half the study population for the first 72 hours. The baseline cardiac index at randomisation was the same in both groups,  $2.23 \text{ L/min/m}^2$ . This increased 4-6 hours after the infusion to  $2.58 \pm 0.69 \text{ L/min/m}^2$  in the levosimendan group versus  $2.46 \pm 0.73 \text{ L/min/m}^2$  in the placebo group. By the end of the first day, values were equivalent at approximately  $2.61 \text{ L/min/m}^2$ , where the values remained for the next 48 hours.

There was no difference in the primary outcome at 30 days; 32 deaths (12.9%) had occurred in the levosimendan groups versus 33 deaths (12.8%) in the placebo group (absolute risk difference (ARR) 0.1%; 95% CI, -5.7 to 5.9;  $P = 0.97$ ). There were no observed significant differences in any of the secondary outcomes. In particular, there was no difference in kidney injury according to RIFLE criteria between groups, with renal replacement initiated in 24 (9.7%) of the levosimendan patients versus 33 (12.8%) of the placebo patients (ARR, -3.1%; 95% CI, -8.6 to 2.4;  $P = 0.27$ ). Duration of mechanical ventilation was similar (levosimendan group, 19 hours vs. placebo group, 21 hours; ARR -2; 95% CI, -5 to 1;  $P = 0.48$ ). Finally, there was no difference in duration of intensive care stay (levosimendan group, 72 hours vs. placebo group, 84 hours; ARR -12, 95% CI, -21 to 2;  $P = 0.08$ ) or hospital length of stay (14 days vs. 14 days; ARR -0; 95% CI, -1 to 2;  $P = 0.39$ ).

## Critique

The CHEETAH trial is the largest randomised control trial investigating the use of levosimendan for treatment of post cardiac surgery myocardial dysfunction. In contrast, the majority of previous studies had concentrated on prophylactic infusions in selected higher risk, mainly low left ventricular ejection fraction populations.<sup>10</sup> The rationale for prophylactic levosimendan was a potential myocardial protective effect via opening of adenosine triphosphate dependent potassium channels.<sup>11</sup> However, using levosimendan after the onset of cardiac dysfunction might be too late to be effective. As levosimendan increases cardiac output without increasing myocardial energy demands, induces coronary artery vasodilation and has a possible lusitropic action, it theoretically has advantages over traditional inotropes, and would seem to have specific advantages for post cardiac surgery patients.

The CHEETAH trial aimed to enrol either patients with an ejection fraction of <25%, and therefore at risk of postoperative myocardial dysfunction, or patients who developed low cardiac output syndrome. By using inclusion criteria in the perioperative period, over 4,725 preoperative patients were consented, which was a massive undertaking as only 647 patients subsequently met the inclusion criteria. A further testament to the commitment of the research team was that only 15 patients were excluded due to logistic reasons. However, 126 patients who had been consented were excluded, for unreported reasons by the attending physician. This meant one in five who met the inclusion criteria were not randomised.

Although the inclusion criteria included low ejection fraction, in reality only 22 patients (4.4%) had an ejection fraction less than <25%. A further 30% of patients required a IABP or inotropes at weaning from bypass but the majority of patients (65%) were enrolled because of postoperative haemodynamic support in the ICU. As the median ejection fraction was a relatively preserved 50%, this is perhaps not the population that a recent meta analysis suggested would benefit from levosimendan,<sup>10</sup> but rather was a population with a newly-acquired need for post operative haemodynamic support. As the trial did not mandate haemodynamic monitoring, it is not clear if this population, at lower risk of low cardiac output syndrome, had developed myocardial dysfunction or vasoplegia or both. Vasoplegic syndrome is relatively common affecting up to 25% of cardiac surgery patients. Almost half the patients in this trial were on noradrenaline, suggesting a need for vasoconstriction.<sup>12</sup> Levosimendan is an inodilator, which has theoretical and perhaps clinical beneficial effects in heart failure;<sup>5</sup> however, in conditions where vasodilation is pathognomonic recent evidence suggests levosimendan may cause harm.<sup>13</sup>

A further inclusion criteria was the requirement for an IABP, which was used in 50 patients in the levosimendan group and 44 patients in the placebo group. The requirement for an IABP was an outcome measure in both the LEVO CTS and LICORN trials, as it was hoped prophylactic levosimendan infusion would obviate the need for mechanical support.<sup>8,9</sup> However, its use as an inclusion criteria, in almost 20% of the CHEETAH population may be problematic. Firstly, there are variations in the indications for insertion, and, secondly, IABPs have similar haemodynamic effects to levosimendan.<sup>14</sup> There is insufficient evidence that levosimendan improves outcome in patients with an IABP already in situ, although cardiac index may moderately increase over IABP alone.<sup>14,15</sup>

Finally, in terms of the population recruited in this trial, the majority of patients in previous trials had coronary artery bypass grafts. In addition to inotropy, levosimendan induces coronary artery dilation, resulting in an increase in blood flow to ischaemic myocardium and enhanced arterial-ventricular coupling.<sup>7,16</sup> The CHEETAH trial enrolled

patients undergoing a variety of procedures. Less than a quarter had isolated CABG, the population which might benefit most from levosimendan. Although the mechanism of injury in terms of cardioplegia and cardiopulmonary bypass may be similar in valve and CABG patients, the investigators acknowledge that myocardial dysfunction may have different pathophysiological features and therefore respond differently to levosimendan. In the LEVO-CTS trial, valve patients had a worse outcome in comparison to CABG patients.<sup>8</sup> This was not evident in this trial, however the isolated CABG patients were in the minority.

A further difference between the CHEETAH and LEVO-CTS<sup>8</sup> and LICORN<sup>9</sup> trials was the dose studied. The CHEETAH protocol stipulated the infusion was commenced without a loading dose at a rate of 0.05 µg/kg/min and titrated up to a maximum of 0.2 µg/kg/min. Dosing regimes have differed in previous trials with some incorporating a loading dose whilst others have not. Current consensus suggests that bolus doses in this patient population are associated with excess hypotension and are currently not recommended, although the bolus in the LEVO-CTS trial was not associated with adverse haemodynamics.<sup>17,8</sup> Adequate haemodynamic responses are reported within 2 - 4 hours without a loading dose.<sup>18</sup> However, the median dose administered in the CHEETAH trial was only 0.07 µg/kg/min. This dose is smaller than any previous levosimendan trial in cardiac surgery patients.<sup>10</sup> The dose in the placebo group was significantly higher, however a difference of 0.01 µg/kg/min seems clinically insignificant. Furthermore, an adjustment of dose was only attempted in 51% of levosimendan patients and 62% of placebo patients. The low dose and relative lack of adjustment could suggest the protocol failed to provide adequate guidance on titration. In effect, the drug was commenced and continued at a low dose, and was not titrated like other inotropes are generally used. Despite this, a dose of 0.05 µg/kg/min has been clinically used in heart failure patients with improvements in stroke volume, cardiac output and reductions in pulmonary artery wedge pressure.<sup>19</sup> Although this response was observed after a bolus, only 50% of patients at this dose had any haemodynamic response and less than 20% had an increase in stroke volume. It is therefore reasonable to question whether this intervention would have significant beneficial haemodynamic effects. This is possibly reflected in the minimal differences in those patients with haemodynamic measurements, in the vasoactive-inotropic scores, in median inotrope doses or in the number of patients on vasoactive agents. Perhaps in order to show a benefit of the intervention, more attention could have been focused on optimising the dose for the individual patient. In the end the trial was stopped with just 50% of the original recruitment target enrolled, due to an interim analysis predicting futility for the primary outcome of 30-day mortality.

## Where this sits in the body of evidence

In the largest multi-centre, randomised controlled trial investigating levosimendan in cardiac surgery, Mehta and colleagues recruited 882 patients with a left ventricular ejection fraction <35% scheduled for cardiac surgery requiring cardiopulmonary bypass.<sup>8</sup> Patients were randomised to either a levosimendan infusion (0.2 µg/kg/min for 1 hour, followed by a dose of 0.1 µg/kg/min for 23 hours) or placebo infusion. There were two primary outcomes, a four component composite of 30-day mortality, requirement for RRT, myocardial infarction by day 5 and use of a mechanical assist device by day 5, and a two component model of 30-day mortality or requirement for a mechanical assist device by day 5. The four-component primary end-point occurred in 105 (24.5%) levosimendan patients and in 103 (24.5%) placebo patients (OR, 1.00; 99% CI, 0.66 to 1.54; P = 0.98). The two-component end-point occurred in 56 (13.1%) levosimendan patients and in 48 (11.4%) placebo patients (OR, 1.18; 96% CI, 0.76 to 1.82; P = 0.45). There was no difference in adverse events.

In the double-blind, randomised controlled LEVO-CTS trial, held in 13 French cardiac surgery units, Cholley et al recruited 336 patients with an ejection fraction <40% scheduled for isolated or combined CABG and randomised them to either a 24 hour infusion of levosimendan (0.1 µg/kg/min) or placebo, after induction of anaesthesia.<sup>9</sup> The primary end point was a composite of requirement for inotropes at 48 hours, need for a mechanical assist device or need for RRT. This occurred in 87 patients (52%) in the levosimendan group and 101 patients (61%) in the placebo group (absolute risk difference, -7%; 95% CI, -17% to 3%; P = 0.15). There was no significant effect in predefined subgroups; ejection fraction <30%, type of surgery, beta blockers or preoperative inotropes or IABP requirement. There were no differences in adverse outcomes, including atrial fibrillation or hypotension.

In a two-centre, randomised control trial, Levin et al recruited 252 patients scheduled for CABG with an ejection fraction <25% and randomised them to either a levosimendan infusion (loading dose 10 µg/kg followed by an infusion at 0.1 µg/kg/min for 23 hours) or placebo infusion.<sup>20</sup> The intervention commenced 24 hours before surgery. Levosimendan patients had a lower mortality (3.9% vs. 12.8%; P < 0.05), lower incidence of low cardiac output syndrome (7.1% vs. 20.8%; P < 0.05) and lower incidence of complicated weaning from cardiopulmonary bypass (2.4% vs. 9.6%; P < 0.05). The levosimendan group also had a lower requirement for inotropes (7.9% vs. 58.4%; P < 0.05), vasopressors (14.2% vs. 45.6%; P < 0.05) and IABP s (6.3% vs. 30.4%; P < 0.05).

In a randomized, double-blind, placebo-controlled study Lahtinen and colleagues randomised 200 patients with a normal ejection fraction scheduled to undergo heart valve, or combined heart valve and CABG surgery, to levosimendan infusion or placebo.

Levosimendan was commenced at the induction of anaesthesia with a 24 µg/kg bolus over 30 min and subsequently infused at 0.2 µg/kg/min for 24 hours. The primary outcome measure was heart failure, defined as a cardiac index < 2.0 L/min/m<sup>2</sup> or failure to wean from bypass.<sup>21</sup> Heart failure was less frequent in the levosimendan group compared to the placebo (15% vs. 58%; P < 0.001). A rescue inotrope was required less frequently in the levosimendan group (RR, 0.11; 95% CI, 0.01 to 0.89), as was the requirement for an IABP (1% vs. 9%; RR, 0.11; 95% CI, 0.01 to 0.87). The levosimendan group suffered more hypotension and had a greater requirement for noradrenaline; 83 vs. 52 patients; P < 0.001. There was no difference in in-hospital or 6-month mortality.

### **Should we routinely use levosimendan for cardiovascular dysfunction after cardiac surgery ?**

No. The CHEETAH trial does not provide evidence to support the use of levosimendan over standard inotropes for haemodynamic support after cardiac surgery.

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## LEVO-CTS

**Mehta R, Leimberger J, van Diepen S, Meza J, Wang A, Jankowichet R et al. Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery. *N Engl J Med* 2017; 376:2032-2042**

### Introduction

Levosimendan is a calcium sensitizing inotropic agent with vasodilator properties. In contrast to catecholamines, levosimendan increases myocardial contraction with minimal increase in myocardial energy demand.<sup>1</sup> Levosimendan also has additional potential beneficial effects, through coronary artery vasodilation and anti-stunning effects on the myocardium.<sup>2,3</sup> Furthermore, these effects are not attenuated by concomitant beta-blockade.<sup>4</sup> As cardiac surgery patients are at risk of transient myocardial depression related to cardiopulmonary bypass, a significant number of patients develop a pathological low cardiac output syndrome associated with increased morbidity and mortality.<sup>5</sup> Patients with pre-existing left ventricular dysfunction are at particular risk of low cardiac output syndrome.<sup>6</sup>

Levosimendan has been successfully used in heart failure patients requiring haemodynamic support.<sup>7</sup> Considering the pharmacological effects and potential clinical benefits in heart failure, levosimendan has been used for both the treatment and prevention of low cardiac output syndrome in a variety of cardiac surgical conditions. A meta-analysis suggested levosimendan was associated with reduced mortality and post-operative complications in patients with low left ventricular ejection fraction.<sup>8</sup> However, the trials were generally small, had varying inclusion criteria and used different infusion regimes. The LEVO-CTS trial was designed to investigate the efficacy of prophylactic levosimendan in a large high-risk cardiac surgery population.

### Synopsis

LEVO-CTS was a multi-centre, randomised controlled trial performed in 70 cardiac surgery units in the United States and Canada. The aim was to investigate a prophylactic levosimendan infusion commenced prior to cardiac surgery on the composite end points of 30-day mortality, requirement for renal replacement therapy (RRT) by day 30, myocardial infarction or need for mechanical cardiac support in the first five days after surgery.

Adult patients with a left ventricular ejection fraction of 35% or less, scheduled for either coronary artery bypass grafting (CABG), aortic or mitral valve surgery, or a combination thereof, and requiring cardiopulmonary bypass, were eligible for recruitment. Patients were excluded if they had pre-existing cardiomyopathy or

pericardial disease, active infection, dialysis dependent renal failure or significant renal dysfunction (eGFR < 30 ml/kg/1.73m<sup>2</sup>) or had a mechanical assist device in-situ or where insertion was planned. Patients were also excluded due to abnormal haemodynamics, defined as a tachycardia greater than 120 bpm or systolic blood pressure less than 90 mm Hg. Patients above 170 kg were not enrolled.

Eligible patients were randomised using a 24 hour web based system without stratification to receive levosimendan or placebo infusion. The infusion dose was patient weight-based, commencing with a loading dose of 0.2 µg/kg/min for 1 hour, followed by an infusion of 0.1 µg/kg/min for a further 23 hours. Patient management was subsequently at the discretion of the treating physician, including the use of other vasoactive medications.

There were two primary outcome measures; firstly, a composite of mortality at 30 days, requirement for RRT at 30 days, myocardial infarction and the use of a mechanical cardiac assist device in the five days after surgery; and secondly, a composite of mortality at 30 days and the use of a mechanical assist device, again in the five days post surgery. Secondary endpoints included the incidence of low cardiac output syndrome, the need for inotropes beyond 24 hours and post operative ICU length of stay. Low cardiac output syndrome was defined as the requirement for a mechanical assist device, or two consecutive post operative low cardiac output measurements (< 2.0 L/min/m<sup>2</sup>), or one low cardiac output measurement plus the use of at least two inotropes beyond 24 hours. Safety measurements included the incidence of hypotension (mean arterial pressure < 60 mm Hg), new atrial fibrillation, ventricular arrhythmias, stroke, cardiac arrest, and mortality at 90 days.

Assuming an estimated four component composite event rate of 32% in the placebo group, a total sample size of 760 patients was required to provide 80% power to detect a 35% relative reduction in events in the levosimendan group, at the 0.01 significance level. The sample size was increased to 880 patients after enrolment of 600 patients due to a lower than expected event rate.

A total of 956 patients were screened, of which 882 were randomised, with 442 allocated to the levosimendan group and 440 to the placebo group. The main reason for exclusion was failure to meet the ejection fraction criteria. Baseline characteristics were similar in the two groups; patients were mainly white (90%) and male (80%), with a median age of 65 years. They had multiple co-morbidities, with over half having a previous myocardial infarction. Both groups had similar rates of diabetes, and a third suffered from chronic kidney disease. Around 80% had documented heart failure and the median ejection fraction was 27%.

Cardiopulmonary bypass was used in all but one patient. 66.3% of patients underwent isolated CABG, whilst the majority of the remaining operations were either mitral or aortic valve repairs combined with CABG. The median duration of cardiopulmonary bypass was 112 minutes.

A total of 849 patients received the prescribed intervention with 428 in the levosimendan and 421 in the placebo group. The majority of infusions (96%) were commenced prior to surgery with a median time of 0.33 hours before knife-to-skin. The infusion was continued for 24 hours in 80.6% of the levosimendan group and 85.0% in the placebo group. A total of 67 patients (15.6%) in the levosimendan group and 48 patients (11.4%) in the placebo received the infusion for less than the planned time. The infusion was prematurely permanently discontinued in 28 levosimendan patients and in 24 placebo patients. The majority of infusion interruptions or discontinuations in both groups were due to hypotension. In the 699 patients who had cardiac output measurements, the cardiac index was significantly higher in the levosimendan group ( $2.86 \pm 0.61$  vs.  $2.68 \pm 0.65$  L/min/m<sup>2</sup>;  $P < 0.001$ ).

There was no difference in either of the primary end-points. The four component end-point occurred in 105 patients (24.5%) in the levosimendan group and in 103 patients (24.5%) in the placebo group (adjusted odds ratio, 1.00; 99% CI, 0.66 to 1.54;  $P = 0.98$ ), whilst the two component end-point occurred in 56 (13.1%) levosimendan patients and 48 (11.4%) patients in the placebo group (adjusted odds ratio, 1.18; 96% CI, 0.76 to 1.82;  $P = 0.45$ ). Furthermore, there were no differences in the primary outcomes in any pre-specified sub-groups, although there may have been a signal towards better outcome in patients with lower ejection fractions. Secondary outcomes were considered exploratory due to the equivocal primary outcome results. Again, there was no difference in length of ICU stay (2.8 vs. 2.9 days;  $P = 0.25$ ), although there were significant differences in the incidence of low cardiac output syndrome (78 vs. 108; OR, 0.62; 95% CI, 0.44 to 0.88;  $P = 0.007$ ) and inotrope use beyond 24 hrs (235 vs. 264; OR, 0.71; 95% CI, 0.53 to 0.94;  $P = 0.02$ ) in favour of the levosimendan group. There were no significant differences in the pre-specified safety end points, although mortality was lower at 90 days in the levosimendan group (4.7% vs. 7.1%; unadjusted hazard ratio, 0.64; 95% CI, 0.37 to 1.13;  $P = 0.12$ ).

## Critique

The LEVO-CTS trial was one of several studies this year investigating the effects of levosimendan in cardiac surgery patients. Both LEVO-CTS and LICORN<sup>9</sup> investigated the effect of prophylactic levosimendan infusions commenced after induction of anaesthesia, but before surgery commenced, while the CHEETAH trial<sup>10</sup> examined the effect of levosimendan on postoperative patients who had developed low cardiac

output syndrome. In contrast to previous meta analyses, the results of these recent large multi-centre trials have not demonstrated a beneficial effect of levosimendan compared with placebo in a mixed population of cardiac surgery patients.<sup>8</sup> Although previous smaller trials have suggested benefit, larger, more recent, and more robust trials have failed to demonstrate any convincing efficacy of levosimendan in this patient group. When the 2016 LeoPARDS trial<sup>20</sup>, evaluating levosimendan in sepsis, is also taken into account, this brings to four the number of robust randomised controlled trials reporting no benefit from levosimendan above usual care. Indeed, LeoPARDS suggested levosimendan may be harmful in sepsis.

LEVO-CTS is the largest trial investigating the use of prophylactic levosimendan in cardiac surgery patients. It was a well designed, multi-centre trial, but despite randomising 882 patients, the trial was not powered to detect a mortality difference. It is arguable this is one of the most important outcomes for a patient undergoing surgery and the trialists acknowledge this limitation. A trial powered for mortality was planned in the original protocol but would have required around 3,000 patients. Yet we are subsequently left with a result suggesting a possible signal towards reduced mortality at 90 days in the levosimendan group (4.7% vs. 7.1%), although the absolute numbers are low (n=20 vs. n=30). Therein lies a fundamental problem with cardiac surgery research, which has seen a decline in mortality to less than 2%. The trialists attempt to circumvent this problem by using a composite end point of 30-day mortality, requirement for RRT at 30 days, myocardial infarction and the use of a mechanical assist device by day five after surgery.

Use of composite outcomes increases the number of events in a trial, thus increasing power. The individual endpoints are clinically relevant and perhaps arguably reflect the perceived benefits of levosimendan in terms of inotropy, anti-ischaemic and renal protective effects. However, there are other cardiovascular outcomes that although subsequently reported could equally justifiably have been included in the primary composite outcome. In addition, the use of composites has been cautioned as composite results can mask effects on individual outcomes.<sup>11</sup> The individual component were also reported, however the study was not powered to detect important differences. Furthermore, it has been recommended that every single combination of events should be reported.<sup>11</sup>

The inclusion of outcomes with different clinical importance and large variations in frequency can also be problematic. Mortality was low in this population but is clearly more significant to a patient than requirement for postoperative RRT. The frequencies of the individual components were also very different, with mechanical assist devices and myocardial infarction much more common than the other composite outcomes. The

use of mechanical assist devices was lower than in the LICORN trial, a result clouded by the absence of a standardised indication for the use of mechanical assist devices.<sup>9</sup> Perhaps more problematic was the reported incidence of myocardial infarction at approximately 15% in both groups. This individual component contributed to almost half of the events in the trial. The reported rates were more than double the rates reported in the CHEETAH trial and more than six times the reported rates in a similar cohort of low ejection fraction cardiac surgery patients.<sup>10,12</sup> Defining a myocardial infarction after cardiac surgery is difficult, particularly in valve surgery. However, biomarkers are elevated after any cardiac surgery and elevations are associated with poorer outcomes.<sup>13</sup> Recommendations suggest a combination of biomarkers and either ECG or imaging documentation of myocardial damage.<sup>13</sup> The criteria used in the LEVO-CTS study were more liberal than current consensus definitions, making comparisons with similar trials troublesome.

The criteria used for patient selection also raises questions. The trial enrolled patients with an ejection fraction <35% as a high-risk population for subsequent morbidity and mortality. However, the lower the ejection fraction the higher the risk. A recent meta analysis including Levo-CTS, LICORN and CHEETAH suggested that only patients with a more significant reduction in ejection fraction benefit from levosimendan.<sup>14</sup> In enrolling patients with an ejection fraction < 35%, the cohort may not have been of sufficiently high risk to discern a benefit from levosimendan, especially as mortality overall was only 4%. Additionally, there was a possible signal towards better outcomes in patients with lower ejection fraction, defined as <25%.

The selection of patients undergoing valve surgery, with or without CABG, may also have affected these results. A third of patients in this trial had valve surgery; these patients have intrinsically higher risk than revascularisation surgery alone. Levosimendan produces coronary artery vasodilation, with increased blood flow to ischaemic myocardium, and therefore may preferentially benefit CABG patients.<sup>2</sup> Valve-only patients who received levosimendan had the worst outcome in this trial. Prior to this trial, the largest single positive study enrolled patients with a low ejection fraction for CABG only.<sup>15</sup> This study also commenced levosimendan prophylactically, but started the infusion much earlier by admitting patients to the ICU 24 hours before surgery. Subsequently, these patients had significantly higher cardiac index and oxygen delivery prior to surgery than the placebo group. In the LEVO-CTS trial, for practical reasons, the study infusion was commenced only post induction of anaesthesia. A loading dose was administered, which has been shown to have positive haemodynamic effects within one hour of administration.<sup>16</sup> However, myocardial preconditioning, a theoretical benefit of levosimendan in this population, may only be obtained several hours before any insult. Therefore, despite the bolus dose, this potential benefit may have been lost.<sup>17</sup>

A further issue with the dosing regime was that 16% of the levosimendan group did not complete the infusion for the prescribed 24 hours. This appears to be double the rate in the LICORN trial. The predominant reason was because of hypotension, although a similar number of patients receiving placebo also had hypotension.<sup>9</sup> Despite this the trial reported a significant reduction in the incidence of low cardiac output syndrome and the use of inotropes beyond 24 hours after initiation of study drug. Perhaps this is not surprising as the study defined low cardiac output syndrome as either the need for mechanical assist (which wasn't significantly different between the groups) or essentially the need for inotropes beyond 24 hours (which had a significant 7.8% reduction in favour of levosimendan). Given that a 24-hour levosimendan infusion has been shown to have haemodynamic effects well beyond the discontinuation of the infusion, and be potentially superior to 48 hours of dobutamine, it arguable that these reported differences are interesting but not unexpected.<sup>18</sup> Also, there was no difference in the median duration of ICU stay (2.8 vs. 2.9 days) which suggests that residual inotropes at 24 hours were weaned relatively quickly in both groups.

Despite 699 patients reported to have had cardiac output measurements using pulmonary artery catheters, only one result is reported. The cardiac index after the infusion was significantly higher in the levosimendan group ( $2.86 \pm 0.61$  vs.  $2.68 \pm 0.65$  L/min/m<sup>2</sup>). It is difficult to contemplate that this modest increase in cardiac index (both of which are within the "normal" range) could translate into a meaningful benefit in clinical outcome. Perhaps this patient population could have been more optimally chosen to show a benefit from levosimendan, or perhaps, if adequate tissue oxygenation is maintained, the choice of haemodynamic support is less important. Despite its novel mechanism of action and the potential theoretical benefits, it could be time to consider levosimendan like any other inotrope, only more expensive.

### **Where this sits in the body of evidence**

In a double-blind randomised controlled trial in 13 French cardiac surgery units, Cholley et al recruited 336 patients with an ejection fraction <40% scheduled for isolated or combined CABG, and randomised them to either a 24 hour infusion of levosimendan (0.1 µg/kg/min) or placebo after induction of anaesthesia.<sup>9</sup> The primary end point was a composite of requirement for inotropes at 48 hours, need for a mechanical assist device or need for RRT. The primary end point occurred in 87 patients (52%) in the levosimendan group and 101 patients (61%) in the placebo group (absolute risk difference, -7%; 95% CI, -17% to 3%; P = 0.15). There were no significant differences in predefined subgroups: ejection fraction <30%, type of surgery, beta blockade, pre operative inotropes or intra-aortic balloon pump (IABP) requirement. There were no differences in adverse outcomes, including atrial fibrillation or hypotension.

In a two-centre, randomised controlled trial, Levin and colleagues recruited 252 patients with an ejection fraction <25% who were scheduled for CABG, and randomised them to a levosimendan infusion (loading dose 10 µg/kg followed by an infusion at 0.1 µg/kg/min for 23 hours) or placebo infusion.<sup>15</sup> The intervention commenced 24 hours before surgery. The levosimendan patients had a lower mortality (3.9% vs. 12.8%;  $P < 0.05$ ), a lower incidence of low cardiac output syndrome (7.1% vs. 20.8%;  $P < 0.05$ ) and a lower incidence of complicated weaning from cardiopulmonary bypass (2.4% vs. 9.6%;  $P < 0.05$ ). The levosimendan group also had a lower requirement for inotropes (7.9% vs. 58.4%;  $P < 0.05$ ), vasopressors (14.2% vs. 45.6%;  $P < 0.05$ ) and IABPs (6.3% vs. 30.4%;  $P < 0.05$ ).

In a randomized, double-blind, placebo-controlled trial, Lahtinen randomised 200 patients with a normal ejection fraction scheduled to undergo heart valve or combined heart valve and CABG surgery, to levosimendan infusion or placebo.<sup>19</sup> Levosimendan was started at induction of anaesthesia with a 24 µg/kg bolus over 30 min and followed by a infusion at 0.2 µg/kg/min for 24 hours. The primary outcome was heart failure, defined as a cardiac index < 2.0 L/min/m<sup>2</sup> or failure to wean from bypass. Heart failure was less frequent in the levosimendan compared to the placebo (15% vs. 58%;  $P < 0.001$ ). A rescue inotrope was needed less frequently in the levosimendan group (risk ratio, 0.11; 95% CI, 0.01 to 0.89), as was the requirement for an IABP (1% vs. 9%; RR, 0.11; 95% CI, 0.01 to 0.87). The levosimendan group also suffered more hypotension and needed noradrenaline more often; 83 vs. 52 patients,  $P < 0.001$ . There was no difference in in-hospital or 6-month mortality.

In a large multi-centre, randomised placebo-controlled trial, Londoni recruited 506 patients who required peri-operative haemodynamic support after cardiac surgery.<sup>10</sup> Patients were randomised to either levosimendan infusion (0.025 to 0.2 µg/kg/min) or placebo for up to 48 hours. The primary outcome was 30-day mortality. The trial was stopped early for futility. There was no significant difference in 30-day mortality (32 levosimendan patients (12.9%) vs. 33 placebo patients (12.8%); absolute risk difference, 0.1%; 95% CI, -5.7 to 5.9;  $P = 0.97$ ). There was no difference in duration of ventilation, ICU or hospital stay. Nor were there any differences in cardiac arrhythmias or rates of hypotension.

### **Should we routinely use levosimendan prophylactically in high risk cardiac surgical patients?**

No. Prophylactic levosimendan does not appear to provide any patient-centred benefits in this setting.



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## LICORN Study

**Cholley C, Caruba T, Grosjean S, Amour J, Ouattara A Villacorta J et al. Effect of Levosimendan on Low Cardiac Output Syndrome in Patients With Low Ejection Fraction Undergoing Coronary Artery Bypass Grafting With Cardiopulmonary Bypass. The LICORN Randomised Clinical Trial. JAMA 2017;318(6):548-556**

### Introduction

Although mortality after cardiac surgery has steadily declined to 1-2%, this overall low mortality rate conceals a higher risk population with considerably increased mortality.<sup>1</sup> A consistent finding amongst such patients is the presence of reduced left ventricular ejection fraction.<sup>2</sup> Low preoperative ejection fraction is associated with the development of postoperative low cardiac output syndrome.<sup>3</sup> This syndrome is characterised by a variable combination of systolic and diastolic dysfunction leading to reduced cardiac output and oxygen delivery. The syndrome has been defined as a measured cardiac index of  $< 2.2 \text{ L/min/m}^2$ , or in the absence of cardiac output measurement, clinical manifestations consistent with low cardiac output, such as oliguria, low central venous saturation, elevations of lactate, the need for post operative inotropes or mechanical assist device.<sup>4</sup> A more severe form, with associated hypotension (systolic  $< 90 \text{ mm Hg}$ ), is also described.<sup>4</sup>

Outcomes in patients who develop low cardiac output are invariably worse, with increased morbidity and mortality.<sup>1</sup> Treatment consists of haemodynamic support with fluids, inotropes and mechanical assist devices. However, the optimum treatment for the condition remains undefined.<sup>4</sup> In the cardiac surgery setting the use of conventional inotropes has been associated with potential harm.<sup>5</sup> Levosimendan is a calcium sensitizing inotropic drug which increases myocardial contraction with minimal increase in myocardial oxygen demand.<sup>6</sup> A further advantageous effect in the cardiac surgery population is coronary artery dilatation.<sup>7</sup> Levosimendan therefore seems an ideal drug to support the failing heart in the peri-operative cardiac surgery setting. Furthermore, clinical evidence suggested the most beneficial effects were derived by patients with reduced pre-operative ejection fraction.<sup>8</sup> The LICORN trial was one of two trials published this year designed to investigate the effect of a prophylactic levosimendan infusion in cardiac surgery patients.

### Synopsis

LICORN was a multi-centre, randomised, placebo-controlled trial performed in 13 cardiac surgery units in France. The primary aim was to investigate the effect of a prophylactic

levosimendan infusion, commenced before surgery, on the development of low cardiac output syndrome.

Adult patients scheduled for either elective coronary artery bypass grafting (CABG), alone or in combination with valve surgery, who had a left ventricular ejection fraction less than 40% were eligible for recruitment. Patients were excluded if they were pregnant, had pre-existing renal failure (defined as a creatinine clearance < 30 ml/min), liver dysfunction (prothrombin ratio < 50%) or had abnormal haemodynamics, defined as a tachycardia greater than 120 bpm or a mean arterial pressure (MAP) less than 60 mm Hg. Patients who were already receiving preoperative inotropes, or had a prophylactic intra-aortic balloon pump (IABP) inserted, were still eligible.

Randomisation occurred via a secure web based system, with allocation to receive prophylactic levosimendan or placebo infusion. This was stratified by centre, type of surgery, left ventricular ejection fraction (< 30% or 30 - 40%), preoperative inotrope, IABP or beta blocker treatment. The infusion was commenced after induction of anaesthesia at a rate of 0.1 µg/kg/min and continued without adjustment for 24 hours. Drug administration was discontinued due to refractory hypotension (< MAP 60 mm Hg) after optimisation (at anaesthetists discretion), intractable arrhythmias or anaphylaxis.

The primary endpoint was a composite measure chosen to reflect the development of low cardiac output syndrome, namely catecholamine requirement after 48 hours, the need for mechanical assist device (or continued use beyond 96 hours if inserted prophylactically) and the requirement for renal replacement therapy (RRT). Secondary endpoints included the individual components of the primary endpoint, in hospital, 28- and 180- day mortality, length of ICU and hospital stay, ventilator-free days and days out-of-intensive care and out-of-hospital at 28 days. Data on the number of days requiring catecholamines, mechanical assist devices and RRT were also collected. Safety measurements included the incidence of hypotension (MAP < 60 mmHg) and treatment required, as well as the incidence of both arrhythmias and myocardial damage, as reflected by troponin values.

Assuming an estimated 65% event rate in the placebo group, a total sample size of 340 patients was calculated to have 80% power to detect a 15% absolute risk difference at an alpha level of 5%. The primary analysis was performed on an intention-to-treat basis. There were several planned subgroup analyses, including the variation in effect with type of surgery, left ventricular ejection fraction (< 30% and 30-40%), preoperative mechanical assist device or inotropes, and use of preoperative beta blockers.

A total of 336 patients were randomised over a two-year period, with 167 in the levosimendan group and 168 in the placebo group. One person withdrew consent. The baseline characteristics were similar in each group; randomised patients were approximately 68 years of age, mainly male (84%) with an ASA score of three (73%). The majority of patients (78%) had an ejection fraction between 30 and 40%, with a mean of 33% in both groups. Although there were relatively more patients with NYHA class 2 in the levosimendan group (52% vs. 35%), and more class 3 patients in the placebo group (34% vs. 50%), the Euroscore II was similar in each group (levosimendan group, 3.1% vs. placebo group, 3.4%). Groups were similar with regard to preoperative interventions; 10 patients in the levosimendan group were either on inotropes or mechanical assist device versus 8 patients in the placebo group. The majority of patients were receiving beta blockers (80%) and statins (87%).

Cardiopulmonary bypass was used in all but three patients, with 74% of patients having isolated CABG, whilst the majority of the remaining operations were either mitral or aortic valve surgery combined with CABG. The median duration of cardiopulmonary bypass was 89 minutes in the levosimendan group versus 92 minutes in the placebo group. Post surgery, 90% of the levosimendan group required inotropes versus 83% of the placebo group. Ninety-one percent of patients received study drug during the 24 hour intervention. However, seven patients in the placebo group did not receive the infusion, and although all patients in the levosimendan group received the intervention, seven patients had early drug interruption (mainly for hypotension or arrhythmias).

There was no difference in the composite primary end-point, which occurred in 87 (52%) levosimendan patients and in 101 (61%) placebo patients (absolute risk difference, -7%; 95% CI, -17% to 3%;  $P = 0.15$ ). The most frequently occurring component of the composite end-point was the need for inotropes at 48 hours (54% of patients overall). Although this was less frequent in the levosimendan group, this again was not significant (49% vs. 59%; absolute risk difference, -8%; 95% CI, -18% to 1%;  $P = 0.09$ ). The need for a mechanical assist device occurred in 27 levosimendan patients and 25 placebo patients (absolute risk difference, 1%; 95% CI, -6% to 8%;  $P = 0.75$ ), while 15 levosimendan patients required RRT versus 10 in the placebo group (absolute risk difference, 3%; 95% CI, -1% to 7%;  $P = 0.16$ ). There were no interactions in the predefined sub-group analyses for left ventricular ejection <30%, preoperative beta blocker use, type of surgery or preoperative use of mechanical assist devices or inotropes. Furthermore, there were no differences in any of the secondary end points in the study. In terms of safety outcomes, severe hypotension occurred in 57% of the levosimendan group and 48% in the placebo group ( $P = 0.11$ ). Hypotension management was similar in both groups, although more patients in the levosimendan group required interruption of the infusion (5 patients vs. 1 patient) although this was not significant ( $P = 0.12$ ). More patients in the levosimendan

group suffered from atrial fibrillation {83 patients (50%) vs. 68 patients (40%)} although this again was not statistically significant.

## **Critique**

The LICORN trial was conducted during the same period as the LEVO-CTS trial, which also examined the effect of a prophylactic infusion of levosimendan. The trials share many similarities. Both selected a similar population of patients with reduced left ventricular ejection fraction undergoing cardiac surgery requiring cardiopulmonary bypass. Both commenced the levosimendan infusion after induction but before surgery and for a total period of 24 hours. The same infusion dose was administered, although the LEVO-CTS trial incorporated a bolus before infusion. Finally, both trials reported similar outcome measures. Although the larger LEVO-CTS was powered to detect a difference in a derived clinical composite outcome of mortality, need for RRT, myocardial infarction and requirement for a mechanical assist device, the smaller LICORN trial reported the incidence of post-operative low cardiac output syndrome - a secondary outcome in the LEVO-CTS trial. Considering the similarities in methodology, it is perhaps not surprising that the results were relatively congruent, with the exception that the LEVO-CTS reported a significant reduction in the incidence of low cardiac output syndrome, while the reduction in the LICORN trial was not significant. With similar design the LICORN trial also shares some of the limitations of the larger LEVO-CTS trial. However, subtle differences exist and the results of this trial expands our knowledge of the critical care management of the high risk cardiac surgery patient.

Although similar, the selection criteria in the two trials were slightly different. The LICORN trial selected patients with a higher preoperative ejection fraction of <40% in comparison to the <35% in the LEVO-CTS trial. The EUROSCORE II predicted mortality in the LICORN was around 3%, which is only moderately higher than the general cardiac surgery population. The mortality risk increases as ejection fraction declines and meta analysis suggests that levosimendan may be most beneficial in patients with more severe myocardial dysfunction.<sup>10,8</sup> Around 80% of patients had an ejection fraction greater than 30%; therefore, as with the LEVO-CTS trial, the population may not have had sufficient cardiac impairment to benefit from levosimendan over conventional supportive measures. A further criticism of the selection criteria in both trials is the inclusion of patients requiring valve surgery. Levosimendan induces coronary artery vasodilation, in addition its inotropic and vasodilatory effects, and may therefore preferentially benefit patients with primarily coronary artery disease.<sup>7</sup> In the LICORN trial, all patients had CABG, although 26% also had additional surgery (mainly valves). It is unclear if the effects of levosimendan vary depending on the pathophysiology of the myocardial impairment. Finally, in terms of patient selection, as a smaller study the LICORN trial stratified for centre, type of surgery, ejection fraction, preoperative

haemodynamic support and use of beta blockers in order to ensure balanced groups. As intended, this process produced similar groups for these selected prognostic factors, however, patients in the levosimendan group were on average two years older, while the placebo group had a larger proportion of patients with NYHA class three heart failure (50% versus 34%). It is difficult to predict how these differences might have influenced the results of the trial, as both age and NYHA Class are included in the EUROSCORE II risk model which overall was similar in both groups.

As with LEVO-CTS, the LICORN trial was not powered to detect a mortality difference. Both trials used composite outcome measures, which although potentially increased statistical power, their use has been criticised.<sup>11</sup> The LICORN trial used a composite of catecholamine infusion persisting after 48 hours, the need for a mechanical assist device or the need for RRT. These outcomes measures are all clinically relevant and the investigators argue they reflect the development of low cardiac output syndrome. However, the outcomes are not exclusively caused by low cardiac output syndrome. In addition, post-operative heart failure may cause other complications which were not included in the composite measure. A diagnosis of low cardiac output syndrome is defined by haemodynamic measurements or requirement for haemodynamic support and its diagnosis is associated with poorer outcomes, but using it as an outcome measure is possibly less relevant than measurable clinical outcomes.<sup>3</sup> The incidence of so called low cardiac output syndrome in this trial was 56% using the primary end point but only 22% in the LEVO-CTS trial, mainly due to differences in the definition of low cardiac output syndrome. One important caveat remains outstanding though – LEVO-CTS used a bolus of levosimendan prior to commencing an infusion, while LICORN only administered an infusion.

A further problem with these chosen outcomes is the imbalance in the incidence of each outcome measure. The predominant outcome measure was the requirement for inotropes at 48 hours, which occurred in 96% of patients who met the primary end-point (although some patients had more than one component of the composite outcome measure). The LEVO CTS trial reported a significant reduction in inotrope requirements at 24 hours in the levosimendan group (54.9% vs. 62.7%; OR, 0.71; 95% CI, 0.53 to 0.94; P = 0.02). The LICORN trial also reported a reduction (49% versus 59%) but this was not significant. These figures appear coherent and one might surmise that the failure of the LICORN trial to achieve significance might be related to the lack of bolus in the infusion regime. But perhaps the most striking consideration is that the LICORN reported the use of inotropes at 48 hours, a full day after the LEVO CTS trial. Reporting at 48 hours may be more clinically relevant, as 24 hours might be too early to differentiate between temporary myocardial stunning, residual anaesthesia or the early effects of sedatives, and the true development of a low cardiac output state. However, there appears to be a

difference in the duration of inotrope support required in the two trials. Furthermore the duration of ICU stay was longer in the LICORN trial (4 days versus 2.8 days). These differences were observed despite the apparent better ejection fraction in the LICORN population. The surgery in the LICORN also involved a higher proportion of patients having arguably lower risk CABG surgery while the LEVO-CTS had more potentially complex valve procedures. Consistent with this, both the aortic cross clamp time and the bypass times were shorter in the LICORN trial.

Duration of ICU stay can be affected by discharge protocols and bed availability, however mortality was also higher in the LICORN trial (above that predicted by the EUROSCORE II) at 1 month and at longer follow up. These results hint at a possible discrepancy in patient outcomes between the two trials, which could be due to a difference in peri-operative management between North America and France, or possibly the absence of a bolus dose in LICORN, as dosing was the same otherwise between the two trials.

Together, LICORN and LEVO-CTS suggest that levosimendan is not beneficial in a mixed cardiac surgery population. Despite this, perhaps a trial powered to detect a difference in mortality, either by selection of patients who would potentially benefit most, or by conducting a much larger trial, or both, would finally end the levosimendan enigma.

### **Where this sits in the body of evidence**

LEVO-CTS is the largest multi-centre, placebo-controlled trial investigating levosimendan in cardiac surgery. It randomised 882 patients, with a left ventricular ejection fraction <35%, scheduled for cardiac surgery requiring cardiopulmonary bypass, to either a levosimendan infusion (0.2 µg/kg/min for 1 hour, followed by a dose of 0.1 µg/kg/min for 23 hours) or placebo infusion.<sup>9</sup> There were two primary outcomes, a four component composite of 30-day mortality, requirement for RRT, myocardial infarction by day 5 and use of a mechanical assist device by day 5, and a two component model of 30-day mortality or requirement for a mechanical assist device by day 5. The four-component primary end-point occurred in 105 (24.5%) levosimendan patients and in 103 (24.5%) placebo patients (OR, 1.00; 99% CI, 0.66 to 1.54; P = 0.98). The two-component end-point occurred in 56 (13.1%) levosimendan patients and in 48 (11.4%) placebo patients (OR, 1.18; 96% CI, 0.76 to 1.82; P = 0.45). There was no difference in adverse events.

In a large multicentre, randomised placebo controlled trial Londoni et al recruited 506 patients who required peri-operative haemodynamic support after cardiac surgery.<sup>12</sup> Patients were randomised to either levosimendan infusion (0.025 to 0.2 µg/kg/min) or placebo for up to 48 hours. The primary outcome was 30-day mortality. The trial was



stopped early due to futility. There was no significant difference in 30-day mortality (levosimendan group, 12.9% vs. placebo group, 12.8%; absolute risk difference, 0.1%; 95% CI, -5.7 to 5.9;  $P = 0.97$ ). There was no difference in duration of ventilation, ICU or hospital stay. Nor were there any differences in cardiac arrhythmias or rates of hypotension.

In a two-centre, randomised control trial, Levin and colleagues recruited 252 patients with an ejection fraction  $<25\%$  who were scheduled for CABG, and randomised them to a levosimendan infusion (loading dose  $10 \mu\text{g}/\text{kg}$  followed by an infusion at  $0.1 \mu\text{g}/\text{kg}/\text{min}$  for 23 hours) or placebo infusion.<sup>13</sup> The intervention commenced 24 hours before surgery. The levosimendan patients had a lower mortality (3.9% vs. 12.8%;  $P < 0.05$ ), a lower incidence of low cardiac output syndrome (7.1% vs. 20.8%;  $P < 0.05$ ) and a lower incidence of complicated weaning from cardiopulmonary bypass (2.4% vs. 9.6%;  $P < 0.05$ ). The levosimendan group also had a lower requirement for inotropes (7.9% vs. 58.4%;  $P < 0.05$ ), vasopressors (14.2% vs. 45.6%;  $P < 0.05$ ) and IABPs (6.3% vs. 30.4%;  $P < 0.05$ ).

In a randomized, double-blind, placebo-controlled trial, Lahtinen randomised 200 patients with a normal ejection fraction scheduled to undergo heart valve or combined heart valve and CABG surgery, to levosimendan infusion or placebo.<sup>14</sup> Levosimendan was started at induction of anaesthesia with a  $24 \mu\text{g}/\text{kg}$  bolus over 30 min and followed by a infusion at  $0.2 \mu\text{g}/\text{kg}/\text{min}$  for 24 hours. The primary outcome was heart failure, defined as a cardiac index  $< 2.0 \text{ L}/\text{min}/\text{m}^2$  or failure to wean from bypass. Heart failure was less frequent in the levosimendan compared to the placebo (15% vs. 58%;  $P < 0.001$ ). A rescue inotrope was needed less frequently in the levosimendan group (risk ratio, 0.11; 95% CI, 0.01 to 0.89), as was the requirement for an IABP (1% vs. 9%; RR, 0.11; 95% CI, 0.01 to 0.87). The levosimendan group also suffered more hypotension and needed noradrenaline more often; 83 vs. 52 patients,  $P < 0.001$ . There was no difference in in-hospital or 6-month mortality

**Should we routinely use levosimendan pre-operatively in patients with low ejection fraction undergoing CABG with cardiopulmonary bypass?**

No. LICORN provides good evidence levosimendan is not beneficial in this setting

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## TTH48

**Kirkegaard H, Søreide E, Haas I de, Pettilä V, Taccone FS, Arus U, et al.  
Targeted Temperature Management for 48 vs. 24 Hours and Neurologic  
Outcome After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial.  
JAMA 2017;318(4):341–50**

### Introduction

In 2002, two studies published simultaneously in the New England Journal of Medicine changed the complexion of post resuscitation care for patients who had suffered an out-of-hospital cardiac arrest (OHCA).<sup>1,2</sup> When these trials compared therapeutic hypothermia at 32 - 34°C with standard care, they demonstrated improved neurological outcomes in the therapeutic hypothermia group.<sup>1,2</sup> Over the past 15 years, therapeutic hypothermia has become a standard of care and is advocated by the 2015 European Resuscitation Council Guidelines.<sup>3</sup> A number of trials have attempted to define the optimal cooling strategy, looking at which patient groups will benefit, when cooling should be initiated, what the optimal target temperature is, and finally, how long patients should be cooled for and the optimal rate of rewarming.<sup>4</sup> Trials investigating therapeutic hypothermia have demonstrated improved neurological outcomes in adults following OHCA, and neonates with hypoxic-ischaemic encephalopathy.<sup>1,2,5,6</sup> Four major studies, involving approximately 3,000 patients, have shown no survival benefit in commencing cooling pre-hospital in comparison to therapeutic hypothermia initiated on arrival to hospital.<sup>7-10</sup>

Two major questions remain surround the “dose” of therapeutic hypothermia; what is the optimal depth and duration of cooling? Studies which demonstrated improved outcomes in patients treated with therapeutic hypothermia can be criticised for the high rates of pyrexia in the control groups.<sup>1,2</sup> The Targeted Temperature Management (TTM) trial addressed this by comparing cooling to 33°C with 36°C (i.e. avoidance of pyrexia). This trial showed similar rates of survival, and survival with a good neurological outcome, whether managed at 33°C or 36°C.<sup>5</sup> The upcoming TTM2 trial (NCT02908308) will compare 33°C to normothermia with early treatment of fever ( $\geq 37.8^\circ\text{C}$ ). The largest gap in the evidence base relates to the optimal duration of therapeutic hypothermia. Bernard and colleagues applied therapeutic hypothermia for 12 hours with active rewarming between hours 18 and 24, whereas, the HACA investigators maintained a temperature of 32 - 34°C for 24 hours followed by 8 hours of passive rewarming.<sup>1,2</sup> The TTM trial applied cooling to 33°C or 36°C for 24 hours with temperature controlled to  $< 37.5^\circ\text{C}$  for a total of 72 hours.<sup>5</sup> The TTH48 trial goes further than any previous study in an adult OHCA population, comparing 24 and 48 hours of therapeutic hypothermia. It is

noteworthy that the trial began before the publication of the TTM trial, hence the choice of 33°C as a target temperature.

## Synopsis

In this multi-centre, randomised controlled trial, two durations of therapeutic hypothermia, either 24 or 48 hours, at 33°C, were compared in patients with return of spontaneous circulation (ROSC) after OHCA. It was hypothesised that 48 hours of therapeutic hypothermia would result in superior neurological outcomes at six months. Patients who suffered an OHCA of presumed cardiac aetiology, had a Glasgow Coma Scale score less than eight following ROSC and were aged  $\geq 18$  years and  $< 80$  years were eligible. Patients with both shockable and non-shockable rhythms were included. Amongst the exclusion criteria were unwitnessed collapse and a presenting rhythm of asystole, OHCA of  $> 60$  minutes duration, cardiovascular instability despite pharmacological support or intra-aortic balloon pump, cerebral vascular events and terminal illness.

The intervention consisted of cooling patients to  $33 \pm 1^\circ\text{C}$  for 48 hours. This was compared to a control group where patients were cooled to  $33 \pm 1^\circ\text{C}$  for 24 hours. The start time of this 24 or 48 hour intervention was the time the patient first achieved a temperature  $\leq 34^\circ\text{C}$ . Both groups were rewarmed at  $0.5^\circ\text{C}/\text{h}$  until  $37^\circ\text{C}$ . In this pragmatic trial, the methods of achieving and maintaining target temperature were not stipulated. There was no predefined time frame in which patients had to reach their target temperature but initiation of cooling within 60 minutes was desirable. Once patients achieved a temperature of  $\leq 34^\circ\text{C}$ , clinicians had 23 hours to recruit and randomise the patients. Patients were treated for a minimum of 72 hours after normothermia was achieved except in cases of unsurvivable multi-organ failure or brainstem death. Where complications arose that may have been attributable to, or exacerbated by, cooling, patients could be rewarmed. These complications included bleeding, life-threatening arrhythmias, or persistent low cardiac output.

Randomisation occurred in a 1:1 manner. There was stratification for age ( $< 60$  vs.  $\geq 60$  years), shockable vs. non-shockable rhythm and study site. Treating clinicians and those collecting data were aware of the treatment allocation, however, outcome assessors were blinded. Researchers had no input into early neuroprognostication or decisions regarding continuation or withdrawal of life sustaining therapies. Clinicians were encouraged to following guidelines on neuroprognostication endorsed by The Danish Society of Intensive Care Medicine and The Danish Society of Anaesthesiology and Intensive Care Medicine.

The primary outcome measure was good neurological outcome at six months. This was defined as Cerebral Performance Categories (CPC) score of one (good cerebral performance) or two (moderate cerebral disability which equates to patients being able to live independently or perform part time work). Secondary outcome measures included six month mortality and time to death. Power calculations were based on an expected 15% absolute increase in the number of patients with a good neurological outcome at six months from 50% to 65%. A two sided P-value of 0.05 was set. To observe this difference 338 patients were required to achieve a power of 80%. The investigators aimed to recruit 355 patients to allow for loss to follow up. A modified intention-to-treat analysis was performed with those who initiated their treatment but withdrew consent being excluded. An adjusted analysis was undertaken using a Cox proportional hazards model. A large number of *a priori* subgroup analyses were performed. As no adjustment to the p-value for multiple comparisons was made, these outcomes should be considered as exploratory.

The study was conducted in 10 ICUs from 6 European countries. Between 2013 and 2016, 907 patients who had suffered an OHCA were screened, with 361 patients ineligible. In total, 355 patients were recruited and 351 were included in the modified intention-to-treat analysis; 175 in the 48-hour group and 176 in the 24-hour group. Patient demographics and arrest characteristics were similar for the two groups. A typical patient was a male in their early 60s with a co-morbidity such as previous ischaemic heart disease, chronic obstructive pulmonary disease or diabetes mellitus. Approximately half of OHCA occurred in the patients own home and only one in ten were unwitnessed. A high proportion of patients had arrest characteristics associated with favourable neurological outcomes: 83% had bystander CPR, 89% had a shockable rhythm and the rate of automated external defibrillator (AED) use was 23%. The median time from collapse to basic life support, advanced life support and ROSC were one, eight and 20 minutes, respectively. A high proportion of patients received immediate coronary angiography (83%) or coronary intervention (41%).

The baseline temperatures in the two groups were similar;  $35 \pm 1.1^{\circ}\text{C}$  vs.  $34.9 \pm 1.0^{\circ}\text{C}$  in the 48-hour and 24-hour groups, respectively. The time to achieve the target temperature of  $\leq 34^{\circ}\text{C}$  following ROSC was 39 minutes shorter in the 48-hour group; 281 (IQR, 217 to 360) minutes compared to 320 (IQR, 241 to 410) minutes in the 24-hour group ( $P = 0.01$ ). There was no significant difference in the mean temperature during the intervention period;  $33.1 \pm 0.5^{\circ}\text{C}$  vs.  $33.0 \pm 0.5^{\circ}\text{C}$  in the 48-hour and 24-hour groups, respectively ( $P = 0.66$ ). The method of achieving therapeutic hypothermia was similar in the two groups, with intravascular cooling (62%), surface cooling (44%) and cold intravenous fluids (35%) being the commonest methods (patients may have received a combination of methods). There was no significant difference in the rate of rewarming

following the intervention period;  $0.3 \pm 0.2^{\circ}\text{C}/\text{hrs}$  vs.  $0.4 \pm 0.2^{\circ}\text{C}/\text{hrs}$  in the 48-hour and 24-hour groups, respectively ( $P = 0.07$ ). Once rewarming commenced in the 24-hour group, a difference emerged in temperatures between the two groups, with excellent separation from hours 32 to 50.

There was no significant difference in the primary outcome measure. A favourable neurological outcome was seen in 69% (95% CI, 62% to 75%) of patients in the 48-hour group and 64% (95% CI, 56% to 71%) in the 24-hour group (RR, 1.08; 95% CI, 0.93 to 1.25;  $P = 0.33$ ). This lack of difference was consistent across all pre-defined subgroups and in a per-protocol analysis. There was no significant difference in the secondary outcome measure of mortality at six months; 27% (95% CI, 21% to 34%) vs. 34% (95% CI, 27% to 41%) in the 48-hour and 24-hour groups, respectively (RR, 0.81; 95% CI, 0.59 to 1.11;  $P = 0.19$ ). No difference in ICU or hospital mortality was seen. The duration of mechanical ventilation was longer by 26 hours and ICU stay longer by 28 hours in the 48-hour group than the 24-hour group (both  $P < 0.001$ ). The rate of adverse events was higher in the 48-hour group, 97% vs. 91% (relative risk, 1.06; 95% CI, 1.01 to 1.12;  $P = 0.04$ ).

## Critique

This was an excellent study with very little to criticise and much to admire. The accompanying editorial is equally insightful.<sup>4</sup> In comparing 48 to 24-hours of therapeutic hypothermia, TTH48 tried to answer an important question regarding the optimal 'dose' of hypothermia. This had strong biological rationale. Patients in the standard care arm of the HACA trial had an average temperature consistently above  $37^{\circ}\text{C}$  from hours 8 to 48 after ROSC.<sup>1</sup> Following cardiac arrest, changes in cerebral blood flow (CBF) and cerebral metabolic rate (CMR) go through four phases. In phase IV, which begins at approximately 24 hours, low, normal or increased CBF may be seen.<sup>11</sup> Studies examining CBF following cardiac arrest have demonstrated that non-survivors had a higher CBF than survivors ( $P < 0.01$ ), with the peak CBF occurring 18 to 30 hours post arrest.<sup>12</sup> On a macroscopic level, therapeutic hypothermia reduces the inflammation that ensues after OHCA, attenuating hyperemia and delayed hypoperfusion. On a cellular level, it reduces oxygen consumption, ATP utilisation and cellular apoptosis.<sup>13</sup> It would seem that doubling of the 'dose' of hypothermia from 24 to 48 hours would potentially benefit patients in this period of hyperaemia and afford a reasonable chance of detecting a difference should one exist.<sup>4</sup>

There are a number of features that are indicative of the quality of this trial. Of the 907 screened patients, only 44 potential participants were missed due to lack of available research staff. The remainder of patients not enrolled were either not eligible or refused to give consent. Only one patient was lost to follow up. The care patients received was remarkable; 83% received bystander CPR, the rate of AED use was 23%, 83% underwent

coronary angiography, 41% had a coronary intervention and the target temperature was reached at approximately 5 hours post cardiac arrest. Although this was a selected group of patients who had survived to ICU admission, nevertheless, these rates of bystander interventions appear high, even by Danish standards (where 228 of the 351 patients were recruited). The Danish cardiac arrest registry revealed that, in 2010, 44.9% (95% CI, 42.6% to 47.1%) of all OHCA patients received bystander CPR and an AED was used in 2.2% [95% CI, 1.5% to 2.9%] of cases.<sup>14</sup> Furthermore, although this trial included both patients with shockable and non-shockable rhythms, only 40 of the 351 patients enrolled had a non-shockable rhythm. By the way of contrast, in the TTM trial, 19% of patients had a non-shockable rhythm.<sup>5</sup> It is unclear why a trial which recruited almost all eligible patients had such a low rate of participants with a non-shockable rhythm. This poses the question, are the participants in this trial representative of the OHCA patients seen in many ICUs?

This high quality care and inclusion of patients with factors associated with a good neurological prognosis culminated in 64% to 69% of patients being alive with a CPC score of one or two at six months. This was higher than any of the three previous studies where typically 50% of patients treated with therapeutic hypothermia survived with a good neurological outcome.<sup>1,2,5</sup> The number of patients alive at six months but with severe disability, coma or vegetative state was small, just 11 out of 243. Accordingly, the higher than expected survival in the 24-hour group meant there was a 5% difference in survival with good neurological outcome at six months. Although this may be clinically relevant, the trial was not powered to detect such a small difference. When every other aspect of cardiac arrest management and post resuscitation care has been optimised it may be that prolonged therapeutic hypothermia has limited scope to influence outcomes.

It is unclear whether an increased duration of cooling would be beneficial in a group with more severe brain injury or a poorer prognosis. Only 38 patients did not have bystander CPR or an emergency service witnessed OHCA, and just 40 patients had a non-shockable rhythm. These cohorts of patients have poorer neurological outcomes, but with such small subgroups it is difficult to draw any meaningful conclusion about the treatment effect of 48 hours of therapeutic hypothermia.<sup>15</sup> This is evidenced by the wide confidence intervals, meaning the estimation of the treatment effect is imprecise; the risk ratio of good neurological outcome in patients with a non-shockable rhythm was 0.61 (95% CI, 0.23 to 1.56) in favour of the 24-hour group.

The investigators recognise that by powering the study to detect a 15% absolute difference in survival with a good neurological outcome at six months there is an appreciable risk of a type II error. It may have been unrealistic to expect that a further 24



hours of therapeutic hypothermia would produce such a large treatment effect. The HACA trial, which compared 32 - 34°C to standard care, only observed a 16% absolute increase in favourable neurological outcome.<sup>1,4</sup> As the TTH48 trial observed a 5% increase in survival with a good neurological outcome, it was estimated that to power a trial to detect this level of difference, 3000 patients would be required. This would be approximately double the number of patients recruited into all trials examining cooling in adult OHCA to date, and vastly exceeds the targeted recruitment of 1900 patients for the upcoming TTM2 trial.<sup>1,2,5</sup> As such this trial may have missed a small but clinically relevant difference.

Overall, this was an excellent study, which was well conducted and provided exemplary care. However, the number of patients who were likely to have a poor neurological outcome was low. This limits the generalisability of the results of this study somewhat.

### **Where this sits in the body of evidence**

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 (target 32 - 34°C) was 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 vs. 39% in the normothermia group (RR, 1.40; 95% CI, 1.08 to 1.81). After adjustment for baseline imbalances hypothermia was associated with reduced mortality (RR, 0.62; 95% CI, 0.36 to 0.95).<sup>1</sup>

Bernard et al randomised 77 patients with an OHCA due to VF, who achieved ROSC but remained comatose, to normothermia (target temperature 37°C) or cooling to 33°C. Patients were cooled for 12 hours with active rewarming between hours 18 and 24. At six hours there was a large separation 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).<sup>2</sup>

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 no difference in 180 day 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

endpoint 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).<sup>5</sup>

The THAPCA-IH trial randomised 329 children aged 38 weeks to 18 years to therapeutic hypothermia ( $33.0 \pm 1.0^\circ\text{C}$  for 48 hours followed by maintenance of normothermia up to 120 hours) or normothermia following in-hospital cardiac arrest (IHCA). Patients were required to be dependant on mechanical ventilation after ROSC and within 6 hours of ROSC. There was no significant difference in the primary outcome measure of favourable neurobehavioral score at 12 months between the two groups; 36% vs. 39% in the hypothermia and normothermia groups, respectively (RR, 0.92; 95% CI, 0.67 to 1.27; P = 0.63). The investigators intended to recruit 558 patients but the trial was terminated early following an interim analysis on the basis of futility.<sup>16</sup>

The THAPCA-OH trial examined cooling after OHCA and recruited patients from 38 ICUs in the United States and Canada. 295 children who remained comatose after OHCA were allocated to therapeutic hypothermia ( $33.0 \pm 1.0^\circ\text{C}$ ) or therapeutic normothermia ( $36.75 \pm 0.75^\circ\text{C}$ ). The treatment was commenced within 6 hours of ROSC. In contrast to the THAPCA-IH trial, the children in this trial were older (median age 2 years), 52% had no pre-existing medical conditions and 72% had a respiratory cause for their cardiac arrest. Asystole was the initial rhythm in 58% of cases. There was no difference in the primary outcome measure of survival at 12 months with a favourable neurobehavioral score; hypothermia group, 20% vs. normothermia group, 12% (RR, 1.54; 95% CI, 0.86 to 2.76; P = 0.14). There was no difference in survival at 12 months; 38% vs. 29% in the hypothermia and normothermia groups respectively (P = 0.13).<sup>17</sup>

The RINSE trial compared standard care with intra-arrest cooling achieved by administration of cold intravenous saline ( $3^\circ\text{C}$ ) in patients who had suffered OHCA. The trial was terminated early after recruitment of 1,198 of a planned 2512 patients due to changes in in-hospital temperature targets following the publication of the TTM trial.<sup>5</sup> The temperature on arrival to hospital 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). 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).<sup>7</sup>

In a study of 1,359 patients with OHCA who achieved ROSC, participants were randomised to standard care or 2 L of intravenous saline at  $4^\circ\text{C}$ . Intravenous cold saline decreased patient temperature by 1.2 to  $1.3^\circ\text{C}$  and reduced the mean time to reach  $34^\circ\text{C}$

( $P < 0.001$ ). 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% vs. 21%;  $P = 0.008$ ).<sup>8</sup>

### **Should we routinely provide therapeutic hypothermia at 33°C for 48 hours post OHCA?**

Not at this time, although there is a clear signal which warrants an adequately powered trial.

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## THAPCA-IH

**Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, et al. Therapeutic Hypothermia after In-Hospital Cardiac Arrest in Children. *N Engl J Med* 2017;376(4):318–29**

### Introduction

Cardiac arrest creates a global ischaemic insult, with return of circulation resulting in an ischaemia - reperfusion injury.<sup>1</sup> In 2002, two major studies demonstrated that the use of therapeutic hypothermia, in comparison to standard care, improved neurological outcomes and mortality in adult patients who had suffered an out-of-hospital cardiac arrest (OHCA).<sup>2,3</sup> In a large study of neonatal hypoxic encephalopathy, cooling to 33.5°C resulted in a 28% relative risk reduction in rates of death or moderate-to-severe disability in comparison to temperature control of 36.5°C to 37°C.<sup>4</sup> Subsequently, the largest trial on temperature management in OHCA in adults demonstrated that targeted temperature management (TTM, 36°C) resulted in similar outcomes to therapeutic hypothermia (33°C).<sup>5</sup>

The use of cooling post OHCA in a paediatric population has recently been studied.<sup>6</sup> In 2015, the Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest in Children trial (THAPCA-OH) compared therapeutic hypothermia (target temperature, 33.0°C) with therapeutic normothermia (target temperature, 36.8°C) and found no statistically significant differences in survival with a good neurological outcome or survival at one year.<sup>6</sup> There is a paucity of evidence for cooling in paediatric patients who have suffered an in-hospital cardiac arrest. Two retrospective cohort studies examined the effect of therapeutic hypothermia in a paediatric population who had suffered either an in-hospital or out-of-hospital cardiac arrest. After correction for confounding variables, these cohort studies demonstrated that therapeutic hypothermia provided no survival benefit.<sup>7,8</sup> However, due to the low quality of evidence in the paediatric population, a trial evaluating the use of temperature control following in-hospital cardiac arrest was needed.

### Synopsis

This randomised, controlled trial compared two temperature management strategies in paediatric patients who had suffered in-hospital cardiac arrest. It was conducted in the USA, Canada, and the United Kingdom and recruited patients from 37 paediatric ICUs. Children aged between 48 hours (with a corrected gestational age  $\geq$  38 weeks) and 18 years who had suffered an in-hospital cardiac arrest and achieved return of spontaneous circulation (ROSC) were eligible if they met the following criteria; duration of chest compressions  $>$  2 minutes, dependant on mechanical ventilation after ROSC and within 6

hours of ROSC. There were 21 exclusion criteria, including; traumatic cardiac arrest, prior cardiac arrest during this hospital stay, a motor score of 5-6 in the Glasgow Coma Scale, severe active bleeding, the need for adrenaline or noradrenaline at  $\geq 2 \mu\text{g}/\text{kg}/\text{minute}$ , a life expectancy of  $< 12$  months or lack of commitment to full treatment.

Patients were randomised to receive 120 hours of therapeutic hypothermia (target temperature,  $33.0 \pm 1.0^\circ\text{C}$ ) or therapeutic normothermia (target temperature,  $36.75 \pm 0.75^\circ\text{C}$ ) in a 1:1 manner using permuted blocks. There was stratification based on age ( $< 2$  years, 2 to  $< 12$  years, or  $\geq 12$  years) and treatment centre. The temperature management of both groups is described in table 3.

	<b>Therapeutic hypothermia (<math>33.0 \pm 1.0^\circ\text{C}</math>)</b>	<b>Therapeutic normothermia (<math>36.75 \pm 0.75^\circ\text{C}</math>)</b>
<b>Temperature Target</b>	<p><b>0 – 48 Hours</b></p> <ul style="list-style-type: none"> <li>• Maintained at <math>33.0 \pm 1.0^\circ\text{C}</math></li> </ul> <p><b>48 to 64 Hours</b></p> <ul style="list-style-type: none"> <li>• Rewarmed to <math>36.75 \pm 0.75^\circ\text{C}</math></li> </ul> <p><b>64 – 120 Hours</b></p> <ul style="list-style-type: none"> <li>• Maintained at <math>36.75 \pm 0.75^\circ\text{C}</math></li> </ul>	<p><b>0 – 120 Hours</b></p> <ul style="list-style-type: none"> <li>• Maintained at <math>36.75 \pm 0.75^\circ\text{C}</math></li> </ul>
<b>Methods of Temperature Control</b>	<p>Dual core temperature measurements Blanketrol III Temperature Management Unit</p>	
<b>Sedation</b>	<p>Midazolam &amp; fentanyl with cisatracurium paralysis</p>	

**Table 3. Temperature management strategies**

The primary outcome measure was survival with a favourable neurobehavioral score at 12 months, defined as an age corrected Vineland Adaptive Behaviour Scale, second edition (VABS-II) of  $\geq 70$  (range 20 to 160, with higher score indicating a better outcome and 100 representing the mean score). At 12 months, the VABS-II score was assessed by a semi-structured interview. At enrolment parents / caregivers completed a questionnaire to ascertain a baseline VABS-II score, children with a score of  $< 70$  were excluded from the primary analysis. In cases where a baseline VABS-II score could not be obtained, patients could be included in the primary analysis provided they scored either one (normal) or two (mild disability) in both the Paediatric Overall Performance Category (POPC) and Paediatric Cerebral Performance Category (PCPC) scores. Secondary outcomes included 12 month survival and change in VABS-II from baseline to 12 months. There were a number of safety outcome measures.

The investigators calculated that 558 patients would need to be recruited to detect a 15% absolute difference in the primary outcome measure, in favour of the hypothermia group, with 90% power. A two sided alpha level of 0.05 was set for the primary analysis and 0.025 for the secondary analysis. The power calculation was based on the assumptions that 35% to 55% of patients in the normothermia group would have a favourable outcome, 5% of patients would be excluded for baseline VABS-II of < 70 and a further 5% would be lost to follow up. A modified intention-to-treat analysis was used.

Between 2009 and 2015, 2,791 patients were screened, 746 were deemed eligible and 329 were randomised; 166 to therapeutic hypothermia and 163 to therapeutic normothermia. Of the patients who were eligible but not included, 214 families declined to give consent, and in 133 cases consent was not sought as doctors did not feel it was appropriate. The trial was terminated early following an interim analysis on the basis of futility.

The two groups were well balanced at baseline. The median age was 1.4 (IQR 0.3 to 5.7) years and 0.6 (0.2 to 6.3) years in the hypothermia and normothermia groups, respectively, 91% of patients had a pre-existing medical condition with over half having congenital heart disease. Two thirds of cardiac arrests were attributed to a primary cardiac cause. Non-shockable rhythms accounted for the majority of cardiac arrests; bradycardia (58%), asystole (7%) and pulseless electrical activity (21%). Just 10% of cases were due to ventricular fibrillation or pulseless ventricular tachycardia, in 4% of cases the cause was unknown. The median time from cardiac arrest to CPR was 0 minutes in both groups. The median duration of CPR was 23.0 minutes (IQR 7.0 to 42.0) and 22.0 minutes (IQR 7.0 to 51.0) in the hypothermia and normothermia groups, respectively. Extracorporeal membrane oxygenation (ECMO) was used in 55% of patients after cardiac arrest.

Extrapolating from the supplementary material, there was excellent separation between the two groups from hours 8 to 56. It is notable that pyrexia (> 38°C) was consistently avoided in both groups. The times to achieve the target temperature are given in table 4.

Sixty patients with as baseline VABS-II score of < 70 were excluded from the primary analysis and 12 patients were lost to follow up; therefore, the primary outcome measure was reported in 257 patients. There was no significant difference in the the number of patients alive at 12 months with a VABS-II score  $\geq$  70; 36% vs. 39% in the hypothermia and normothermia groups, respectively (RR, 0.92; 95% CI, 0.67 to 1.27; P = 0.63). This result was unchanged in sensitivity, per-protocol and subgroup analyses.

	<b>Therapeutic hypothermia (33.0 ± 1.0°C)</b>	<b>Therapeutic normothermia (36.75 ± 0.75°C)</b>
<b>Median baseline temperature</b>	35.7°C (IQR 34.4 to 37.0)	36.0°C (IQR 34.7 to 37.0)
<b>Median time from ROSC to initiation of treatment</b>	4.9 hours (IQR 3.9 to 5.8)	4.7 hours (IQR 4.0 to 5.7)
<b>Median time from initiation of treatment to reach target temperature for &gt; 1 hour</b>	2.1 hours (IQR 1.5 to 3.5)	2.0 hours (IQR 1.1 to 3.1)
<b>Total duration in target temperature range</b>	<b>Maintenance 33.0 ± 1.0°C</b> 48.0 hours (IQR 48.0 to 48.0) <b>Rewarming 36.75 ± 0.75°C</b> 17.5 hours (IQR 15.1 to 18.5) <b>Maintenance &lt; 36.75°C</b> 52.0 hours (IQR 50.0 to 54.5)	<b>Maintenance &lt; 36.75°C</b> 120 hours (IQR 120.0 to 120.0)

**Table 4. Time to achieve target temperature**

In the secondary outcomes, there was no difference in change from baseline VABS-II score between the two groups ( $P = 0.70$ ). Approximately one third of patients demonstrated an improvement in VABS-II score or a change of  $\leq 15$ . There was no difference in the number of patients alive at one year; 49% vs. 46% in the hypothermia and normothermia groups, respectively (RR, 1.07; 95% CI, 0.85 to 1.34;  $P = 0.56$ ). There was no statistical difference in pre-defined safety outcomes between the two groups.

## Critique

The THAPCA-IH trial is the first study to examine the role of temperature management in the setting of in-hospital paediatric cardiac arrest. It is a clinically important topic that warranted investigation, as pre-existing evidence from adults or paediatric OHCA is difficult to extrapolate to this group of patients. The participants in this trial are markedly different to those in the previous THAPCA-OH trial: patients were younger (median one year of age, compared to two years), they were more likely to have a pre-existing medical condition (91% compared to 48%), more likely to have a cardiac cause of their arrest (65% compared to 11%) and were typically bradycardic as opposed to asystolic at the time of presentation.<sup>6</sup>

In the THAPCA-OH trial, the majority of patients died as a result of withdrawal of life sustaining treatment due to poor neurological prognosis (82% of the hypothermia group and 79% of the normothermia group).<sup>6</sup> This is in contrast to the THAPCA-IH trial, where



withdrawal of care was on the basis of poor neurological prognosis in 36% of cases, and cardiovascular failure in 34% of cases. The reasons for these differences are likely to be multifactorial. There was no protocol in place for neuroprognostication or withdrawal of life sustaining treatment in either THAPCA trial, but as these trials ran concurrently in the same centres this was unlikely to have been a factor. The high rate of asphyxial cardiac arrest in the THAPCA-OH trial (72%), accompanied by a greater delay before commencement of CPR, may have resulted a higher incidence of hypoxic brain injury.<sup>6</sup> In the THAPCA-IH trial, 61% of patients arrested whilst in ICU, 65% had a cardiac cause for their arrest, and 55% of patients were treated with ECMO. This suggests a significant number of patients may have had a heart that was failing even prior to their arrest. Thus, it appears the two THAPCA trials investigated very different patient cohorts.

THAPCA-IH was well conducted as evidenced by: the multi-centre international design, the mandatory three day training sessions for hospital staff that was repeated annually, the excellent temperature separation between the two groups, the low rate of protocol violations (8 patients) and low rates of loss to follow up (12 patients). In addition, the end points were relevant to patients and their care givers, namely: survival with good neurological outcome (VABS-II), measures of learning (Mullen Early Learning Composite) and intelligence (Wechsler Abbreviated Scale of Intelligence).

Ultimately, the major weakness of this trial is that it was terminated early due to futility and thus was underpowered having recruited 329 of the 558 planned patients. However, there was no signal of benefit or harm either for the entire population or any patient subgroup. More eligible patients were missed because families declined to give consent (n = 214) or because clinicians felt it was not appropriate to approach families (n = 133), than were actually recruited. This exemplifies the challenges clinicians face conducting research in the field of paediatric cardiac arrest.

The temperature management in this trial warrants discussion. Importantly, in both study arms great effort was made to avoid pyrexia. At 120 hours, the duration of temperature control exceeds that used in either adult studies of cardiac arrest (24 to 72 hours) or neonatal studies of hypoxia encephalopathy (78 hours).<sup>2-5</sup> However, one potential source of criticism was the time required to initiate cooling; six to seven hours had lapsed before patients reached their target temperature. The ischaemia - reperfusion injury that creates the Post Cardiac Arrest Syndrome begins within minutes of cardiac arrest. Cooling has beneficial effects on cerebral blood flow and metabolic rate, reduces the number of excitatory amino acids and decreases apoptosis.<sup>4</sup> Thus, it seems intuitive that early cooling would be beneficial. In the THAPCA-IH trial 61% of patients were already in an ICU setting at the time of the cardiac arrest and the median time to initiation of CPR was zero minutes. This presented a unique set of circumstances

that may have allowed early cooling. This begs the question, was this a missed opportunity to initiate early temperature management?

To date, trials of pre-hospital cooling using pressurised ice cold intravenous fluids have demonstrated no benefit, and potential harm.<sup>9,10</sup> This may be attributable to the 66% reduction in coronary blood flow that occurs with rapid infusion of pressurised cold fluids in cardiac arrest.<sup>11,12</sup> In the context of in-hospital cardiac arrest the application of surface cooling would obviate the negative effects that pressurised cold fluids have on coronary perfusion. The consent process may have contributed to the delay in initiation of temperature control, though it is understandable that the investigators would seek informed consent in advance in the challenging area of paediatric cardiac arrest. A model of deferred consent may be beneficial in future studies.

Studies in adult and neonatal populations which have shown benefit with therapeutic hypothermia have permitted pyrexia in the control arm.<sup>2-4</sup> The two THAPCA trials were ultimately trials of two temperature management strategies; hypothermia and normothermia, both of which avoided pyrexia. As such, they are analogous to the TTM trial in adults.<sup>5</sup> Although the THAPCA-IH trial was underpowered, its findings are consistent with the body of evidence that hypothermia delivers similar results as normothermia provided pyrexia is avoided.

### **Where this sits in the body of evidence**

The THAPCA-OH trial, which examined cooling after OHCA, recruited patients from 38 ICUs in the US and Canada. 295 children who remained comatose after OHCA were allocated to therapeutic hypothermia ( $33.0 \pm 1.0^{\circ}\text{C}$ ) or therapeutic normothermia ( $36.75 \pm 0.75^{\circ}\text{C}$ ). The treatment was commenced within 6 hours of ROSC. The primary outcome measure of survival at 12 months with a VABS-II score  $\geq 70$  was evaluable in 260 children. In contrast to the THAPCA-IH trial, the children in this trial were older (median age 2 years), 52% had no pre-existing medical conditions and 72% had a respiratory cause for their cardiac arrest. Asystole was the initial rhythm in 58% of cases. There was no difference in the primary outcome measure; hypothermia group, 20% vs. normothermia group, 12% (RR, 1.54; 95% CI, 0.86 to 2.76;  $P = 0.14$ ). There was no difference in change in VABS-II score ( $P = 0.13$ ) or survival at 12 months; 38% vs. 29% in the hypothermia and normothermia groups respectively ( $P = 0.13$ ).<sup>6</sup>

A randomised controlled trial examined the effect of whole body cooling in 208 term neonates with hypoxia encephalopathy. Potential cases were identified based on neonates with a cord pH  $< 7.0$  / base deficit  $> 16$  mmol/L or a pH  $< 7.15$  / base deficit 10 - 15.9 mmol/L plus an acute perinatal event, and Apgar score  $\leq 5$  or requirement for mechanical ventilation. Once these criteria were met, infants were screened for

encephalopathy and enrolled if present. Infants were assigned to either surface cooling to 33.5°C or radiant warming to 36.5°C and 37.0°C. The intervention was commenced within 6 hours and continued for 72 hours followed by at least 6 hours of active rewarming. Notably, 41 / 106 in the control group had a temperature > 38°C during the treatment period. Infants were evaluated at 18 to 22 months, the primary outcome measure of death or moderate to severe disability occurred in 44% of the hypothermia group and 62% of the control group (RR, 0.72; 95% CI, 0.54 to 0.95, P = 0.01).<sup>4</sup>

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). The average temperature in the control group was consistently above 37°C from hours 8 to 48 after ROSC.<sup>2</sup>

Bernard et al randomised 77 Patients with an OHCA due to VF, who achieved ROSC but remained comatose, to normothermia (target temperature 37°C) or cooling (target temperature 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 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).<sup>3</sup>

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 no difference in 180-day 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).<sup>5</sup>

A single centre retrospective cohort study examined the effect of cooling on paediatric cardiac arrest (91% of arrests were asphyxial and 52% occurred in hospital). Of the 181

cases studied, 40 had therapeutic hypothermia with a median target temperature 34.0°C (33.5 to 34.8°C) applied for 24 hours. There was no difference in hospital mortality between the therapeutic hypothermia and standard care groups (55.0% vs. 55.3%;  $P \approx 1.0$ ) or rates of discharge to home (78% vs. 68%  $P = 0.46$ ). Hypothermia was more likely to be applied in cases of unwitnessed arrest or where higher doses of adrenaline were used to achieve ROSC. After adjustment for these variables, hypothermia was not associated with a decrease in mortality (OR 0.47,  $P = 0.2$ ).<sup>7</sup>

A multi-centre retrospective study from Canada and the UK compared the effects of hypothermia ( $n = 29$ ) with normothermia ( $n = 50$ ) on post cardiac arrest outcomes (both in-hospital cardiac arrest and OHCA). In accordance with guidelines, pyrexia was avoided in the normothermia group. In the hypothermia group, the mean temperature achieved was  $33.7 \pm 1.3^\circ\text{C}$  and cooling was applied for  $20.8 \pm 11.9$  hours. Hypothermia was associated with a greater duration of cardiac arrest (30 minutes vs. 10;  $P = 0.002$ ), more doses of adrenaline ( $P = 0.006$ ) and higher median post resuscitation lactate (16.2 vs. 7.5 mmol/L;  $P < 0.001$ ). The crude mortality was higher in the hypothermia group (69.0%) than in the normothermia group (38.0%), (OR 3.62; 95% CI, 1.37 to 9.62;  $P = 0.009$ ). However, once adjustments were made for baseline imbalances, there was no difference in mortality between the two groups ( $P=0.502$ ).<sup>8</sup>

### **Should we routinely use prolonged therapeutic hypothermia at 33°C post in-hospital paediatric cardiac arrest?**

No. Targeting 33°C does not seem to be beneficial in comparison to normothermia provided pyrexia is avoided.

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## INPRESS

**Futier E, Lefrant J-Y, Guinot P-G, Godet T, Lorne E, Cuvillon P, et al. Effect of Individualized vs. Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. JAMA 2017;318(14):1346-57**

### Introduction

Current guidelines recommend that patients are safe to proceed to elective surgery if their systolic blood pressure (SBP) is < 160 mm Hg and diastolic blood pressure (DBP) is < 100 mm Hg in the primary care setting or SBP < 180 mm Hg and DBP < 110 mm Hg in the secondary care setting.<sup>1</sup> In patients with SBP < 180 mm Hg and DBP < 110 mm Hg who have no evidence of end organ dysfunction, there is little evidence of additional perioperative cardiovascular risk.<sup>1</sup> Higher levels of hypertension are, however, associated with poorer perioperative outcomes. In a case series of 209,985 patients, 10% had preoperative hypertension. There was a two fold increase in rates of elevated troponin or in-hospital mortality in those with SBP > 200 mm Hg. It is unclear whether this risk is modifiable. A total of 69 cases were cancelled for hypertension (mean blood pressure (BP) 203 / 111 mm Hg) and subsequently rescheduled, when these patients represented for surgery their BP was only marginally improved (mean BP 192 / 102 mm Hg).<sup>2</sup>

Despite the harm associated with profound preoperative hypertension, the appropriate blood pressure target under general anaesthesia is unknown. Data on 33,000 general anaesthesia cases was analysed and found that both depth and duration of intraoperative hypotension were associated with the development of ischaemic complications.<sup>3</sup> The risk of acute kidney injury (AKI) increased if a mean arterial pressure (MAP) < 60 mm Hg was observed at any point. The risk of AKI increased with increasing duration of hypotension. The risk of myocardial injury increased with a MAP < 55 mm Hg, but no increase in risk was seen beyond 10 minutes duration.<sup>3</sup> The threshold for harm is altered in a cohort of patients with chronic hypertension. For every 10 mm Hg decrease in mean intraoperative DBP, the risk of elevated troponin or in-hospital mortality increases (odds ratio, 1.26; 95% CI, 1.07 to 1.48; P = 0.005).<sup>2</sup> Conversely, postoperative delirium is associated with intraoperative BP variance but not absolute or relative hypotension.<sup>4</sup> With so little known about the threshold for harm from intraoperative hypotension, and whether this can be modified by vasopressors, a study into intraoperative blood pressure management was warranted.

### Synopsis

The Intraoperative Norepinephrine to control arterial PRESSure (INPRESS) study investigators hypothesised that using individualised blood pressure targets would result

in a reduction in postoperative organ dysfunction when compared to standard care. This investigator-initiated, multi-centre, open-label, randomised controlled trial was conducted in nine French hospitals. The investigators sought to identify a cohort of patients who were at high risk of postoperative organ dysfunction. Patients scheduled to undergo surgery, expected to last > 2 hours under general anaesthetic, were eligible provided they met all the following criteria: age  $\geq$  50 years, American Society of Anaesthesiologists (ASA) physical status  $\geq$  II and  $\geq$  4 elements of acute kidney injury risk index present.<sup>5</sup> Exclusion criteria were SBP  $\geq$ 180 mm Hg, DBP  $\geq$  110 mm Hg, decompensated heart failure, acute coronary syndrome, sepsis or vasopressor dependence preoperatively, chronic kidney disease stage IV or worse (glomerular filtration rate < 30 mL/min/1.73 m<sup>2</sup>) or renovascular surgery.

Patients were randomised to one of two groups. The intervention consisted of SBP targeted to within  $\pm$  10% of resting SBP (taken at the time of preoperative anaesthetic assessment) using norepinephrine (2.5 mg in 250 mL 0.9% NaCl administered via a dedicated peripheral intravenous line). In the usual care arm SBP < 80mm Hg or > 40% below resting SBP was treated using 6 mg ephedrine boluses (to a maximum of 60 mg, if further vasopressor was needed noradrenaline was used). Both groups had a radial arterial line sited. The intervention commenced intraoperatively and ran for four hours postoperatively.

Patients had a standardised maintenance fluid regimen of lactated Ringers solution at 4 mL/kg/hr. 250 mL fluid boluses of 6% hydroxyethyl starch in 0.9% saline (molecular weight of 130 kDa, substitution ratio of 0.4) were given over 10 minutes to achieve a maximal stroke volume index (SVI). If the SVI increased by more than 10% then the fluid bolus was repeated. If the SVI failed to increase by > 10% this was deemed the maximal SVI (termed refSVI). During to course of the surgery if SVI fell by > 10% a repeat fluid bolus was given.

The primary outcome measure was a composite of systemic inflammatory response syndrome (SIRS) plus the occurrence of organ dysfunction (Table 5) at any point in the first seven days. Other secondary outcomes included individual components of the primary outcome measure, ICU and hospital length of stay, rates of surgical complications and mortality. Patients were followed up for 30 days postoperatively. The investigators assumed a 40% risk of the primary outcome occurring in the standard treatment strategy group. Based on a 20% absolute reduction in the primary outcome, 268 patients would be needed to achieve a 95% power with a 2-sided  $\alpha$  level of 0.05. The investigators aimed to recruit 300 patients to account for loss to follow up and protocol deviations. No adjustments were made for multiple comparisons. Analysis was on an intention-to-treat basis. Patients were consented preoperatively and randomised in a 1:1

manner with stratification based on study site, urgency of surgery, and surgical site. Although the intraoperative team and those collecting intraoperative data could not be blinded, those providing post operative care beyond the intervention period and outcome assessors were unaware of the treatment allocation.

<b>System</b>	<b>Definition</b>
<b>Renal</b>	presence of any level of AKI according to RIFLE criteria. Equates to > 1.5 increase in creatinine or UO < 0.5 ml/kg/hr for 6 hours
<b>Respiratory</b>	need for invasive or non-invasive ventilation
<b>Cardiovascular</b>	acute cardiac failure or myocardial ischaemia or infarction
<b>Neurological</b>	stroke or Glasgow Coma Scale score ≤ 14
<b>Coagulation</b>	platelets < 100 x 10 <sup>3</sup> /mm <sup>3</sup>

**Table 5. Definitions used to identify organ dysfunction**

A total of 1,494 patients were screened. After appropriate exclusions, 300 patients were recruited and 298 were randomised. The majority of the 1,194 exclusions (n = 810) were because patients did not meet the acute kidney injury risk criteria. Following withdrawals of consent, cancelled surgery and exclusion for incorrect randomisation, 292 patients were included in the primary analysis. The groups were well balanced. Patients were typically male (84.9%), ASA II (39.7%) or III (59.2%), had a mean age of 70 years, and were undergoing abdominal surgery (95.2%) which was typically elective in nature (84.6%) and lasting four to five hours. Hypertension (82.2%) and diabetes mellitus (51.4%) were the commonest co-morbidities. The baseline SBP was 135 mm Hg in both groups.

During surgery, the mean SBP was higher in the individualised treatment group than the standard treatment group; 123 (SD 25) mm Hg vs. 116 (SD 24) mm Hg, difference 6.5 mm Hg (95% CI, 3.8 to 9.2). Throughout the intervention period the SBP was consistently higher in the individualised treatment group (P < 0.001). At the end of the intervention period the SBP was greater in the individualised treatment group than the standard treatment group; 120 (SD 22) mm Hg vs. 110 (SD 19) mm Hg (P < 0.001). The same was true for the DBP (60 (SD 10) mm Hg vs. 56 (SD 9) mm Hg P < 0.001) and MAP (81 (SD 14) mm Hg vs. 75 (SD 13) mm Hg (P < 0.001). In the standard treatment group, 26.2% of patients required rescue norepinephrine. The median volume of maintenance crystalloid fluid administered intraoperatively was higher in the standard treatment group (2000 mL, IQR 1500 to 2500) than the individualised treatment group (1500 mL, IQR 1000 to 2000 mL) (P < 0.001). There was no difference in the cumulative volume of crystalloid



given over the intervention period (P 0.09), the volume of colloid given (P = 0.25), or blood products used (P = 0.28).

Those randomised to the individualised treatment group demonstrated a statistically significant reduction in SIRS plus organ dysfunction; (56 / 147) 38.1% vs. (75 / 145) 51.7% (relative risk, 0.73; 95% CI, 0.56 to 0.94; P = 0.02). The majority of this difference was due to an additional 23 cases of AKI observed in the standard treatment group (adjusted relative risk (ARR), 0.70; 95% CI, 0.53 to 0.92; P = 0.01). The secondary outcomes measures should be considered as hypothesis generating only. Of the 35 quoted secondary outcomes with P values, four complications were less common in the individualised treatment group: altered level of consciousness (ARR, 0.34; 95% CI 0.16 to 0.75; P = 0.007), pneumonia (ARR 0.38; 95%, CI 0.15 to 0.93; P = 0.03), sepsis (ARR 0.54; 95% CI, 0.34 to 0.86; P = 0.009) and surgical site infection (ARR 0.63; 95% CI, 0.40 to 0.98; P = 0.04). There was no difference in 30 day mortality between the two groups (ARR, 1.11; 95% CI, 0.44 to 2.81; P = 0.82). There was no difference in rates of adverse events.

## Critique

This thought-provoking trial investigated a fundamental element of perioperative care about which surprisingly little is known. The trial was well conducted, including a focus on standardisation to remove extremes of practice. Fluid balance was tightly controlled and closely recorded, reducing its effects as a confounding variable. There was complete follow up of patients. The investigators acknowledge rates of sepsis, pneumonia and wound infection are higher than previously published for patients undergoing laparotomies of comparable duration.<sup>6</sup> However, the patients enrolled were at high risk of post operative organ dysfunction, with 56.5% requiring high dependency care postoperatively.

It is important to point out that this was not a pragmatic study that purely targeted blood pressure management. The investigators mandated maximum and minimum doses of induction agents, use of inhalational agents for maintenance of anaesthesia, ventilator settings, haemoglobin targets, bispectral index (BIS) targets, and prohibited the use of epidural anaesthesia intra-operatively and a number of drugs, including NSIADs.

The population of patients recruited into this study were typically hypertensive, undergoing abdominal surgery (95.2%) under elective conditions (84.6%). The investigators recommended that patients be treated in accordance with national guidelines. Current French guidelines, published mid way through the trial recruitment period, recommend the use of Enhanced Recovery After Surgery (ERAS) programmes in elective abdominal surgery. These recommend that patients should not receive colonic

preparation, that ASA I and II patients receive oral carbohydrate rich isotonic fluids preoperatively and that intraoperative fluid administration is based on “parameters reflecting volume replacement” (with oesophageal doppler monitoring the least invasive method of aiding fluid management).<sup>7</sup> In this trial, all patients had some form of cardiac monitor capable of cardiac output / stroke volume monitoring (personal correspondence with the author). The actual monitor used was not recorded. Studies have demonstrated poor correlation in paired stroke volume measurements ( $r = 0.39$ ) when two different brands of cardiac output monitors are used in the same patient undergoing abdominal surgery using an ERAS programme.<sup>8</sup> The impact of this is unclear, though the investigators point out there was no differences in outcomes between hospitals.

The investigators did not collect data on which patients were managed using an ERAS pathway. The number of patients receiving bowel preparation, the fasting time of patients and the use of oral carbohydrate rich isotonic fluids was not recorded (personal correspondence with author). The baseline volaemic status of patients is a major unknown variable. AKI formed part of the composite primary outcome measure. Patients undergoing abdominal surgery using an ERAS programme have lower urine outputs on the first three days postoperatively than those treated with standard care ( $P < 0.05$ ).<sup>9</sup> Yet they have fewer perioperative complications (RR 0.54, 95% CI, 0.42 to 0.69) and shorter lengths of hospital stay.<sup>9,10</sup> Knowledge regarding rates of ERAS in either intervention arm would have been helpful given the fragility of the result; a reduction in just three events in the standard treatment arm (for example three patients with a higher urinary output) would render the result for the primary outcome measure no longer statistically significant.

Although there was a reduction in the primary outcome measure in the individualised treatment group, this was a composite measure where outcomes were not of equal importance to patients. The presence of thrombocytopenia or six hours of a reduced urine output will be of less significance to a patient than a stroke or myocardial infarction. The majority of difference in the primary outcome measure was due to an additional 23 cases of AKI observed in the standard treatment group (“risk”, 13 cases; “injury”, 10 cases; need for renal replacement therapy (RRT), 1 case). Although AKI has been associated with prolonged hospital stay and increased hospital mortality, this was not observed in this study.<sup>11</sup>

The investigators attempted to answer an important question; what is the correct blood pressure target for high risk patients undergoing major surgery? In doing so they eloquently demonstrated how little we now know about the deleterious effects of hypotension. The excess in postoperative complications could be attributed to hypotension in the standard treatment group, but it is unclear from this trial whether it

is the absolute depth or duration of hypotension that is harmful.<sup>2-4</sup> The investigators acknowledge this as a weakness. A so-called 'triple low effect' may exist where a combination of intraoperative hypotension, deep hypnotic level and requirement for low levels of anaesthesia is associated with an increase in mortality.<sup>12</sup> It has been demonstrated that each minute spent with a SBP < 80 mm Hg is associated with an increase in one year mortality (OR, 1.036; 95% CI, 1.006 to 1.066; P = 0.0125).<sup>13</sup> It may be that a different SBP threshold should have been chosen in the standard treatment group (for example 100 mm Hg). This may be enough to reduce the complication rate, obviating the need for individualised targets.

By comparing noradrenaline (which predominantly acts as an  $\alpha$ -adrenoceptor agonist) with ephedrine (which has greater  $\beta$ -adrenergic effects), a significant confounding variable has been introduced. We do not know what mediated the benefit in the individualised treatment group. There are a number of possibilities; achieving an individualised blood pressure target, venoconstriction with improved preload, positive inotropy with an increase in cardiac output (though there was no between group difference in the cardiac index) or a combination of all three. Could the beneficial effect of noradrenaline be replicated using an alternative vasopressor? It does appear that the choice of vasopressor may be important; in a retrospective analysis of patients admitted to ICU with septic shock during a period of noradrenaline shortage, in-hospital mortality was significantly higher during period of shortage (39.6%) than times when there was no shortage (35.9%), (adjusted odds ratio (AOR), 1.15; 95% CI, 1.01 to 1.30; P = 0.03).<sup>14</sup> Similarly ephedrine may cause harm; it is known to demonstrate tachyphylaxis and at high doses reduce the ability of vascular tissue to vasoconstrict when subsequently exposed to norepinephrine.<sup>15</sup>

The actual separation in SBP between the two groups, although statistically significant, was small, just 6.5 mm Hg (95% CI, 3.8 to 9.2) intraoperatively. In sepsis, targeting a higher MAP over a five day period results in a reduction in AKI in a subgroup of patients with chronic hypertension.<sup>16</sup> So a higher blood pressure target causing a reduction in ischaemic events is consistent with the body of evidence, though it is hard to believe the brief intervention in this study was enough to mediate a difference in outcomes at one week.

In summary, INPRESS examined the effect of individualised blood pressure targets in a high risk group of patients, largely undergoing elective abdominal surgery. The use of ERAS programme may have created potential confounding variables. The excess of ischaemic events in the control group was largely due to higher rates of AKI, which did not translate to meaningful patient centred outcomes. Furthermore the result has a low fragility index. This study has highlighted that further work is required to delineate

appropriate blood pressure targets both perioperatively and in ICU. The 65 Trial (ISRCTN10580502), which will compare permissive hypotension (target MAP 60 - 65 mm Hg) with usual care in an ICU population with vasodilatory shock, will help further our knowledge in this area.

### **Where this sits in the body of evidence**

The SEPSISPAM trial recruited 776 patients with septic shock, refractory to fluid resuscitation and requiring  $> 0.1 \mu\text{g}/\text{Kg}/\text{min}$  of norepinephrine or epinephrine. Patients were randomised to a target blood pressure of 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group).<sup>16</sup> There was no difference in the primary outcome measure of 28 day mortality 36.6% vs. 34.0% in the high-target and low-target groups respectively (hazard ratio, 1.07; 95% CI, 0.84 to 1.38;  $P = 0.57$ ). In the subgroup of patients with chronic hypertension ( $n = 340$ ), fewer patients in the high-target group demonstrated doubling of serum creatinine (38.9% vs. 52.0%,  $P = 0.02$ ) or required RRT (31.7% vs. 42.2%,  $P = 0.046$ ). Unfortunately, the internal validity of this trial is affected by the actual blood pressures achieved, with the low-target group, aiming for a target range of 65 to 70 mm Hg, largely achieving blood pressures of 70 – 75 mm Hg, while the high-target group also over-shot, reaching pressures of 85 – 90 mmHg, instead of the intended 80 – 85 mm Hg. Therefore, this trial compared high with higher blood pressures, rather than standard with high pressures.

In an analysis of 209,985 anaesthetic records examining the effect of BP on perioperative outcomes, 10% of patients had hypertension (SBP  $> 140$  mm Hg or DBP  $> 90$  mm Hg) prior to induction of anaesthesia. The primary outcome measure was elevated troponin within 30 days or in-hospital mortality. In the cohort of hypertensive patients, 1.3% had an elevated troponin or in-hospital mortality compared to 2.8% of patients with a SBP  $> 200$  mm Hg. Hypertension was an independent predictor of the primary outcome measure (for every 10 mm Hg increase in SBP; OR, 1.10; 95% CI 1.02 to 1.19,  $P = 0.016$ ). Intraoperative reductions in DBP  $< 85$  mm Hg also predicted troponin rises or in-hospital mortality (for every 10 mm Hg reduction; OR, 1.26; 95% CI 1.07 to 1.48;  $P = 0.005$ ).<sup>2</sup>

A study of 33,330 cases from the Cleveland Clinic, Ohio looked at the effect of depth and duration of intraoperative hypotension on postoperative complications. A number of different MAP thresholds were used, ranging from 55 to 75 mm Hg. The incidence of AKI was 7.4%, myocardial injury, 2.3%, and cardiac complication, 2.8%. If a total of 6 to 10 minutes was spent with MAP  $< 55$  mm Hg there was an increase in AKI (AOR, 1.19; 95% CI, 1.03 to 1.39), elevated troponin (AOR, 1.47; 95% CI, 1.13 to 1.93) and cardiac complications (AOR, 1.46, 95% CI, 1.17 to 1.83). The rates of complications increased with longer duration of hypotension.<sup>3</sup>

In an effort to delineate risk factors for perioperative AKI, Kheterpal and colleagues examined records for 75,952 operations; 57,080 were used in the derivation cohort and 18,872 in the validation cohort. 762 (1.0%) patients went on to develop AKI defined as creatinine > 177  $\mu\text{mol/L}$  or need for RRT. Intra-peritoneal surgery was the single biggest predictor (adjusted hazard ratio, 3.3; 95% CI 2.4 to 4.7) followed by baseline renal insufficiency, ascites, decompensated cardiac failure, emergency surgery, age > 56 yr, insulin dependant diabetes, hypertension, male sex and finally diabetes requiring oral hypoglycaemic agents.<sup>5</sup>

### **Should we implement this individualised blood pressure strategy into our practice?**

Maybe. Further studies are required to delineate the optimal intraoperative blood pressure target and how best to achieve this.

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## Bystander CPR in Out-of-Hospital Cardiac Arrest

**Kragholm K, Wissenberg M, Mortensen RN, Hansen SM, Malta Hansen C, Thorsteinsson K, et al. Bystander Efforts and 1-Year Outcomes in Out-of-Hospital Cardiac Arrest. *N Engl J Med* 2017;376(18):1737–47**

### Introduction

In patients who suffer out-of-hospital cardiac arrests (OHCA), bystander cardiopulmonary resuscitation (CPR) and defibrillation are associated with a number of improved short term outcomes. Bystanders who intervene result in patients having CPR initiated seven minutes earlier than those who have to wait for emergency medical services (EMS).<sup>1</sup> A prospective observational study has shown the probability of ventricular fibrillation (VF) being the initial rhythm at time of EMS arrival decreases with each passing minute, whereas the probability of asystole increases. Bystander CPR reduces the rate of decline in VF incidence with time.<sup>2</sup> Consequently, bystander CPR results in up to twice as many patients being in a shockable rhythm at the time of arrival of EMS; this, in turn, is a predictor of survival.<sup>1,3</sup> Patients who receive bystander CPR are typically younger, have fewer comorbidities and are more likely to arrest in a public place. Even after adjustment for such prognostic variables, bystander CPR is associated with a two- to four- fold increase in 30-day survival.<sup>1,4</sup> The association between bystander defibrillation and outcome is particularly strong, with up to 74% of patients defibrillated within 3 minutes of OHCA surviving.<sup>5</sup> Yet, little is known about the longer term benefits of bystander interventions in OHCA.

Although bystander interventions in OHCA would appear to be beneficial, analysis of cardiac arrest registries has shown this relationship to be less than straightforward. In Sweden, despite a steady increase in rates of bystander CPR over a 21 year period, a J-shaped survival curve was observed for those who received bystander CPR. This translated into a fall in 30-day survival over the first decade of the study from approximately 13% to 6%.<sup>1</sup> When the three counties in Sweden with the highest 30-day survival were compared to the three with the lowest 30-day survival, there was no difference in the rates of bystander CPR.<sup>6</sup> Between 1992 and 2011, there was a decrease in patients found to be in VF during OHCA (35% to 25%;  $P < 0.0001$ ), despite a doubling in the rate of bystander CPR.<sup>6</sup> Finally, analysis of the Victorian Ambulance Cardiac Arrest Registry revealed that patients in a non-shockable rhythm who had bystander CPR had reduced survival to hospital discharge after adjustment for arrest confounders (odds ratio, 0.76; 95% CI, 0.59 to 0.97;  $P = 0.03$ ).<sup>7</sup> In light of this, a study examining the long term outcomes following bystander CPR in OHCA was warranted.

## Synopsis

The investigators of this retrospective study used the Danish Cardiac Arrest Registry to assess the effect of bystander interventions, namely CPR or defibrillation, on long term outcomes following OHCA. Denmark has a population of approximately 5.5 million. In cases of OHCA, EMS dispatch technicians or paramedics to provide basic life support. In addition, a second team consisting of paramedics or anaesthetists is also dispatched. Since June 2001, there has been mandatory reporting of all OHCA in which resuscitation was attempted to the Utstein-style Danish Cardiac Arrest Registry.

The Danish Cardiac Arrest Registry was used to identify all cases of patients aged  $\geq 18$  years who had suffered an OHCA and survived to 30 days between 2001 and 2012. This registry was used to define arrest characteristics. The Danish Civil Personal Register was used to obtain patient demographics and the Danish National Patient Register was used to ascertain discharge diagnosis and therefore likely causes of the cardiac arrest. Co-morbidities prior to the OHCA were determined using a combination of the Danish National Patient Register and the Danish National Prescription Registry.

There were three primary outcome measures at one year; incidence of anoxic brain damage or nursing home admission; all cause mortality; or a composite outcome of death, anoxic brain damage or nursing home admission (whichever came first). Each patient's unique Civil Personal Registration Number was used to interrogate a number of registries to determine outcomes (Table 6). The exclusion criteria were prior residence in a nursing home or pre-existing anoxic brain damage.

Outcome	Source of information
Anoxic brain damage	International Classification of Diseases, 10th Revision (ICD-10) documented on Danish Civil National Register
Nursing home admission	Danish Civil Personal Register and Statistics Denmark
Death	Danish Cause of Death Register

**Table 6. Registries used to collate outcome information**

In the first instance, logistic regression analysis was used to identify interventions that were associated with increased 30-day survival. Subsequent analysis was performed on those who had survived beyond 30 days. Cox regression analysis was used to ascertain the association between bystander interventions and outcomes at one year. Adjustments were made for baseline patient and cardiac arrest characteristics. As a number of initiatives to improve bystander CPR and post resuscitation care had been undertaken during the study period, correction was also made for year of OHCA.



Over the study period there were 42,089 OHCA. Exclusions totalled 7,630, with the overwhelming majority (n = 4,937) for missing or inaccurate Civil Personal Registration Number. Following exclusions, 34,459 were eligible for analysis of outcomes at 30 days. In total, 2,855 (8.3%) patients survived to 30-days. Of these; 1,069 had bystander CPR; 153 had bystander defibrillation (142 of these also had bystander CPR); 534 had no bystander resuscitation; 771 had an EMS witnessed OHCA; and, 328 had missing data on bystander resuscitation status.

In comparison to no bystander intervention, patients who had bystander CPR had a lower number of co-morbidities and were more likely to have their OHCA in a public place (58.4% vs. 34.7%,  $P < 0.001$ ). Of those who had no bystander resuscitation, 3.0% survived to 30 days. The rates of 30-day survival increased with the following interventions; bystander CPR (11.3%), bystander defibrillation (34.7%) and EMS witnessed OHCA (20.8%). During the 12 year study period, the rate of 30-day survival increased from 3.9% to 12.4%.

	<b>No bystander resuscitation</b> absolute risk (95% CI)	<b>Bystander CPR</b> absolute risk (95% CI)	<b>Bystander defibrillation</b> absolute risk (95% CI)	<b>EMS witnessed</b> absolute risk (95% CI)
<b>Anoxic brain damage or nursing home admission</b>	18.6% (16.0 to 22.2%)	12.1% (10.6% to 14.1%)	8.4% (4.1 to 13.6%)	3.7% (2.5 to 4.9%)
<b>Death</b>	15.5% (12.5 to 18.6%)	8.6% (6.9% to 10.3%)	2.0% (0.0 to 4.2%)	8.9% (6.9% to 9.0%)

**Table 7. Primary outcome measures**

The primary outcome measure of anoxic brain damage or admission to nursing home occurred in 300 patients (10.5%); 260 of these patients had anoxic brain damage and 59 went on to die within the one year follow up period. By one year, 276 patients (9.7%) had died. The absolute risk of the primary outcome measures are shown in table 7. Over the course of the 12 year study period, the rates of bystander CPR ( $P < 0.001$ ) and defibrillation ( $P < 0.001$ ) both increased significantly. This was met with a commensurate decrease in the rates of death beyond 30 days ( $P = 0.009$ ) and anoxic brain damage or admission to nursing home ( $P = 0.001$ ) or the composite outcome of death, anoxic brain damage or admission to nursing home ( $P < 0.001$ ).

Following Cox regression analysis, the risk of brain damage or nursing home admission was significantly lower in those who received bystander CPR (HR, 0.62; 95% CI, 0.47 to 0.82;  $P < 0.001$ ) or bystander defibrillation (HR, 0.45; 95% CI, 0.24 to 0.84;  $P = 0.001$ ). Mortality was also reduced in those who received bystander CPR (HR, 0.70; 95% CI, 0.50 to 0.99;  $P = 0.04$ ) or bystander defibrillation (HR, 0.22; 95% CI, 0.07 to 0.73;  $P = 0.01$ ). There was also a reduction in the composite outcome of anoxic brain damage, nursing home admission or death ( $P < 0.001$  for both the CPR and defibrillation cohorts).

## Critique

This interesting paper furthers our knowledge in relation to long term outcomes following OHCA. It demonstrated that both bystander CPR and defibrillation are associated with a reduction in mortality and improved neurological outcomes. The magnitude of this benefit exceeds that provided by medical interventions, such as administration of amiodarone, lidocaine or adrenaline, or intubation (which may even be harmful).<sup>8-10</sup> This paper emphasises the poor prognosis following OHCA with just 8.3% of eligible patients surviving to 30 days, and approximately one in five of these patients having anoxic brain damage, requiring nursing home admission or dying within a year of their cardiac arrest.

This study has a number of strengths, it examined an initial cohort of 42,089 patients and used robust national registries. Such a task could only be accomplished in a healthcare system such as that in Denmark which holds centralised patient data. The level of effort required to assimilate all this data cannot be underestimated and the investigators must be commended. The study design was appropriate as it would seem unlikely that ethical approval to conduct a randomised controlled trial where one arm of patients were randomised to no bystander CPR would be granted (although a RCT examining a mobile phone dispatch system in an effort to increase bystander CPR has been conducted).<sup>11</sup>

When considering the results of this study, the limitations of using registry based data in a retrospective manner should be borne in mind. For example, 11.7% of patients ( $n = 4,937$ ) were excluded as they had either an invalid or missing civil registration number. Of the 2,855 patients who survived to 30 days, 328 (11.4%) had missing status for bystander CPR or defibrillation. This exceeded the number of people who suffered anoxic brain injury or required nursing home admission. The absence of this basic demographic data highlights the weakness of registry studies.

In addition, although efforts were made to correct for all known variables, the total duration of cardiac arrest was unknown. There is a strong correlation between duration

of resuscitation and neurological outcome (as assessed by the modified Rankin Score).<sup>12</sup> With duration of resuscitation being reduced by bystander CPR or defibrillation.<sup>13</sup>

One of the outcome measures used in this study was anoxic brain damage which occurred in 260 of the 300 patients who suffered the combined outcome of anoxic brain damage or nursing home admission. How this diagnosis was made warrants discussion. The investigators describe the process in Denmark which leads to this diagnosis; national census statements, supported by the Danish Society of Cardiology and the Danish Society of Anesthesiology and Intensive Care Medicine, recommend that patients are reviewed by a neurologist with further brain imaging, an electroencephalogram (EEG) or somatosensory evoked potentials (SSEPs) where indicated. The rate of diagnosis of anoxic brain injury was relatively consistent across the five healthcare regions in Denmark, ranging from 7.6% to 11.5% of survivors. Yet the evidence supporting the clinical, electrophysiological and radiological diagnosis of anoxic brain damage following cardiac arrest is weak.

In an advisory statement on neuroprognostication following cardiac arrest, the European Resuscitation Council state that motor score, pupillary and corneal reflexes and SSEPs are the most robust predictors, but the overall quality of evidence is low.<sup>14</sup> For example, an absent or extensor motor response to pain at 72 hours following ROSC has a sensitivity of 74% (range 68 to 79%) for prediction of poor outcome but a false positive rate of 27% (range 12 to 18%).<sup>14</sup> Pfeifer and colleagues looked at the ability of SSEPs, obtained in ICU, to predict poor neurological outcome at four weeks following cardiac arrest. Although there was strong inter-observer reliability between four experts (kappa-coefficient, 0.76), unfavourable neurological prognosis was only correctly predicted in 63% of cases.<sup>15</sup> It is unclear from the paper which ancillary tests were used to support the clinical diagnosis of anoxic brain damage and at what time point the diagnosis was made.

In a study of patients with vegetative state or minimally conscious state due to either traumatic or non-traumatic brain injury, long term follow up was carried out to establish the time to improved level of consciousness. Of these patients, 58% had complete resolution of confusion. The mean time to resolution of confusion was 11.5 weeks for those who began in a minimally conscious state and 30.1 weeks for those who began in a vegetative state. It is therefore conceivable that patients diagnosed with anoxic brain damage whilst in ICU went on to make a neurological recovery. Crucially of the 260 patients diagnosed with anoxic brain damage, only 45 (17.3%) were subsequently admitted to a nursing home. This raises the question as to what level of functional impairment was associated with this anoxic brain damage. The use of a modified Rankin

Scale or cerebral performance category would have revealed more about the patients true long term outcome.<sup>16,17</sup>

The outcome measure of anoxic brain damage was based on ICD-10 codes. In Denmark, these are determined by physicians when discharging patients and entered by clerical staff onto databases.<sup>18</sup> The use of ICD-10 codes taken from the Danish National Patient Register to derive a Charlson co-morbidity index has been validated. The ICD-10 coding demonstrated a positive predictive value of 82% to 100% to predict the presence of 19 first line co-morbidities, such as HIV or diabetes.<sup>18</sup> However, a Canadian study of ICD-10 code validity in sepsis showed that ICD-10 codes had a sensitivity of 46.4% and specificity of 98.7% in identifying patients who had sepsis in comparison to a review of medical notes.<sup>19</sup> Like sepsis, accurately diagnosing anoxic brain damage challenging, this may have rendered the use of ICD-10 codes less robust than initially thought.

In conclusion, bystander interventions are associated with a reduction in the rate of diagnosis of anoxic brain damage, nursing home admission or death. When analysing this paper, the reader must accept neuroprognostication after cardiac arrest is challenging, the outcome measures used were imprecise and that there will always be weaknesses when using registry data. However, this paper probably represents the highest quality of evidence to date in relation to long term outcomes following bystander interventions in OHCA.

### **Where this sits in the body of evidence**

In a trial aimed at increasing rates of bystander CPR, trained volunteers who were within 500 metres of a suspected OHCA were dispatched by EMS using mobile phone positioning technology.<sup>11</sup> This was compared to standard care. The primary outcome measure was rate of bystander-initiated CPR prior to the arrival of EMS. A total of 9,828 lay volunteers were recruited and trained. 1,808 patients underwent randomisation, 794 were not in cardiac arrest. The rates of bystander-initiated CPR was higher in the treatment group; (188 / 305) 61.6% compared with (172 / 360) 47.8% in the control group (difference, 13.9%; 95% CI, 6.2 to 21.2;  $P < 0.001$ ). The adjusted odds ratio for likelihood of CPR in the treatment group was 1.7 (95% CI, 1.2 to 2.5). There was no difference in 30-day survival; 11.2% in the treatment group compared to 8.6% in the control group ( $P = 0.28$ ).

Hasselqvist-Ax completed an analysis of 22 years worth of data from the Swedish Cardiac Arrest Registry to elucidate the effect of bystander CPR on outcomes.<sup>1</sup> Patients who underwent bystander CPR were younger (69 vs. 74 years,  $P < 0.001$ ), less likely to have collapsed in their own home (55.5% vs. 73.2%;  $P < 0.001$ ), more likely to have a initial shockable rhythm (41.3% vs. 20.7%,  $P < 0.001$ ), but had longer EMS response times

(8 mins vs. 6 mins,  $P < 0.001$ ). After adjustment, the 30-day survival in the group who received bystander CPR remained significantly higher (OR, 2.15; 95% CI, 1.88 to 2.45;  $P < 0.001$ ).

Wissenberg examined OHCA from 2001 to 2010 in 19,468 patients from the Danish Cardiac Arrest Registry.<sup>4</sup> The rates of bystander CPR increased significantly during this period, from 21.1% (95% CI, 18.8% to 23.4%) to 44.9% (95% CI, 42.6% to 47.1%) ( $P < 0.001$ ). However the use of bystander defibrillation remained low at just 2.2% in 2010. Bystander CPR was positively associated with an improved 30-day survival (OR, 4.38; 95% CI, 3.17 to 6.06).

Nehme and colleagues examined data from the Victorian Ambulance Cardiac Arrest Registry including 13,448 cases of bystander-witnessed arrests between January 2000 and June 2014.<sup>7</sup> Patients in a shockable rhythm who had bystander CPR had improved survival to hospital discharge (OR, 1.64; 95% CI, 1.40 to 1.92;  $P < 0.001$ ). However, those in a non-shockable rhythm who had bystander CPR had reduced survival to hospital discharge (OR, 0.76; 95% CI, 0.59 to 0.97;  $P = 0.03$ ).

The Swedish Cardiac Arrest Register was interrogated, looking at all OHCA from 1992 to 2011 ( $n = 59,926$ ).<sup>6</sup> The incidence of VF as a presenting rhythm decreased over the course of the study period from 35% to 25% ( $P < 0.0001$ ). Despite this, 30-day survival improved from 4.8% to 10.7% ( $P < 0.0001$ ). 94% of survivors had a favourable neurological outcome (cerebral performance score of 1 or 2 at discharge).

Rossetti and colleagues performed a prospective, observational study of OHCA survivors treated with therapeutic hypothermia.<sup>20</sup> Patients were evaluated using neurological examination (including brainstem reflexes), electroencephalogram (EEG) and somatosensory evoked potentials (SSEP) between 36 and 72 hours post ROSC. 59% of patients died prior to discharge. In-hospital mortality was accurately predicted by the presence of  $\geq 2$  of the following; bilateral absent SSEP, unreactive EEG, absence of one or more brainstem reflexes, or early myoclonus. The overall sensitivity was 0.79 (95% CI, 0.67 to 0.88) and specificity was 1.00 (95% CI, 0.92 to 1.00). Using the same criteria, the ability to predict good functional recovery (CPC one to two) at three to six months was still good; sensitivity, 0.62 (95% CI, 0.51 to 0.72), specificity, 1.00 (95% CI, 0.86 to 1.00).

### **Should bystander CPR be routinely delivered in OHCA?**

Yes. Although there are other confounding variables, the majority of evidence points towards improved short and long term outcomes with bystander CPR in OHCA.

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## SHENFU

**Zhang Q, Chunsheng L, Shao F, Zhao L, Wang M, Fang Y. Efficacy and Safety of Combination Therapy of Shenfu Injection and Postresuscitation Bundle in Patients With Return of Spontaneous Circulation After In-Hospital Cardiac Arrest: A Randomized, Assessor-Blinded, Controlled Trial. Crit Care Med 2017;45(10):1587-95**

### Introduction

Traditional Chinese Medicine (TCM) developed 2,000 - 3,000 years ago from beliefs which are radically different from those in the West; being based on the concepts of the harmony between the forces of yin and yang, the vital energy Qi, the balance of five fundamental elements and the synergy between the human body and surrounding universe.<sup>1</sup> However, in more recent times there has been considerable convergence. TCM modalities such as acupuncture are widely utilised in the West, and there is significant pharmacological crossover with many western medicines being developed from natural products which were also incorporated into TCM.<sup>2,3</sup> In China there has been an increasing use of biosynthetic chemicals, an adoption of western scientific methods (in part aiming to aid international regulatory body acceptance of home-produced drugs) and Chinese contribution to international clinical trials.<sup>4</sup>

The post-cardiac arrest syndrome (PCAS) developing following successful resuscitation encompasses ischaemia-reperfusion-related abnormalities of the immune, vascular and coagulation systems and contributes to ICU mortality following cardiac arrest.<sup>5</sup> Shenfu injection is formulated from ginseng and aconite in a quality-controlled production process approved by the Chinese Ministry of Public Health, and has multiple potential pharmacological effects attributable to the active ingredients of ginsenosides and aconite alkaloids.<sup>6</sup> Previous work had suggested benefits in patients with septic shock,<sup>7</sup> and the investigator's group had identified potential cardio-protective, antioxidant, neuro-protective and lung-protective effects of shenfu in a porcine model of cardiac arrest.<sup>8,9</sup> The investigators hypothesised that shenfu may benefit adult patients with PCAS.

### Synopsis

Fifty Chinese hospitals enrolled 1,022 patients between 2012 and 2015. Eligible patients had sustained return of spontaneous circulation (ROSC) after an in-hospital cardiac arrest (IHCA). Those with a pre-hospital cardiac arrest, severe pre-existing disease (cardiac, hepatic, neurological, respiratory, cancer or HIV), age <18 years, pregnancy, shenfu allergy or with no available researcher were excluded. Randomisation to intervention or control in a 1:1 ratio was computer-generated and stratified by



investigating centre, age and cause of IHCA in blocks of 8. Treatment group patients received open-label shenfu injection (100 ml twice a day by IV infusion for 14 days). Caregivers were unblinded with no placebo administered to the control group. Outcome assessors were blinded to group allocation. Enrolling centres were directed to use a standard post-resuscitation bundle encompassing therapeutic hypothermia (32°C to 34°C for 24 hours), early angiography in suspected acute coronary syndrome and maintenance of physiology (targeting blood glucose 6-8 mmol/L, mean arterial pressure (MAP) 65-100 mmHg and arterial oxygen saturation (SaO<sub>2</sub>) 92%-96%). A sample size of 500 was calculated to have 80% power, at a 5% significance level, to detect a decrease in the primary outcome of 28-day mortality from 70% to 50% with shenfu injection, allowing for predicted dropouts. 1,022 patients were recruited, with 44 excluded from analysis due to withdrawal of consent. The shenfu injection and control groups comprised of 492 and 486 patients, respectively. Baseline characteristics were well matched: mean age was 65, 75% were male and 93% of the Han race. Cardiovascular premorbid conditions were common with coronary artery disease in 32%.

The cardiac arrest occurred in hospital (in a ward in 47%, ICU or coronary care unit in 28%, emergency department in 20% and theatre in 5%). The presenting rhythm was predominantly asystole (82%) with ventricular fibrillation (VF) in 10% and pulseless electrical activity (PEA) in 8%. It was felt to be of a cardiac cause in 67%, respiratory cause in 23%, pulmonary embolus in 4% and electrolyte disturbance in 5%. Patients in the shenfu group received advanced life support (ALS) after a median of 3 minutes delay for a median (IQR) duration of 13 (6-20) minutes; and received a median of 7.7 (4-12) mg of adrenaline, a median of 48 (20-61) IU of vasopressin, mean (SD) of 2.9 (0.6) mg of atropine and median 100 (60-190) mls of crystalloid. Dopamine was the initial vasopressor, given at a mean of 8.7 (6.3) µg/kg/min with noradrenaline additionally at a median (IQR) of 0.5 (0.2-0.9) µg/kg/min. Patients were sedated during ongoing ALS with propofol (mean (SD) 27.3 (0.5) mg/kg/hr) and midazolam (mean 13.6 (3.9) mg/hr). Almost all patients were comatose and ventilated at ICU admission. 19% of the shenfu group received therapeutic hypothermia and 31% early angiography. There were no significant differences in any of the treatments received by control group patients. Of note however, the median (IQR) duration of cardiac arrest in this group was 19 (9-30) minutes (difference not significant).

Mortality was significantly reduced in the shenfu injection group; both at 28 days (primary outcome: 57% vs. 70%; hazard ratio (HR), 0.61; 95% CI, 0.43 to 0.89; P = 0.009) and at 90 days (secondary outcome: 60% vs. 74%; HR, 0.55; 95% CI, 0.38 to 0.79; P = 0.002). The mortality difference was confirmed by log-rank test analysis of Kaplan-Meier plots. Most (66%) of deaths were due to neurological reasons. Other secondary outcomes were also reported. Of those surviving to ICU discharge, there were

significantly more in the shenfu group with a good functional outcome (Cerebral Performance Category (CPC) 1 (good) or 2 (moderate cerebral disability); 70% vs. 59%;  $P = 0.03$ ). There was also a reduced duration of mechanical ventilation (mean  $8.6 \pm 3.2$  days vs.  $12.7 \pm 7.9$ ,  $P < 0.001$ ) and hospital stay (mean  $8.7 \pm 5.9$  days vs.  $13.2 \pm 8.1$ ) with shenfu injection; and an approximate 50% decrease in hospital costs. At 72 hours post ROSC, those in the shenfu group had measurable physiological differences, with a higher mean MAP and PaO<sub>2</sub> and lower mean HR, blood sugar and serum lactate. There were no serious adverse events reported with shenfu injection.

## Critique

This is an intriguing study with an impressive 'headline' mortality reduction backed up by measurable differences in physiological parameters and functional outcomes. The fragility index for the primary outcome (day 28 mortality) is 34 which is higher than found in most positive critical care trials and suggests that chance is unlikely to be the major contributor, but bias remains a possibility.<sup>10</sup>

There are strengths to the study. Multicentre trials of TCM interventions successfully powered for mortality are uncommon.<sup>11</sup> The technical aspects of the methods of randomisation and statistical analysis were appropriate. Patient characteristics were well described and follow up complete (barring consent withdrawal). There was an attempt to standardise other aspects of post cardiac-arrest care in keeping with international guidelines. This will have reduced confounding variables within the trial, make replication of care in future trials easier and finally allow treating clinicians to decide whether the results of this trial are applicable to their practice. It is therefore worth considering the potential modes of action of shenfu injection (comprising 44 individual ginsenoside and aconite compounds) alongside whether this result can be extrapolated to Western ICU practice.

Over 30 ginsenosides have been identified in ginseng plants, each with differing sugar moieties attached to a four-ring 17-carbon structure. In nature they probably protect the plant from microbial attack.<sup>12</sup> Bioavailability of oral ginsenosides is very low, with lipid emulsions utilised to aid absorption and adding rationality to the IV administration in this study. Ginsenosides are partial agonists at varying steroidal receptors, including glucocorticoid and oestrogen receptors; generally binding with low affinity and potentially reducing excessive stimulation at times of physiological stress. They also tend to stabilise excitatory cells by reducing transmission at a variety of excitatory membrane ion channels and stimulating inhibitory receptors.<sup>13</sup> Ginseng has been highly valued in Eastern medicine for over 2,000 years; animal and in-vitro studies have identified anti-inflammatory, antioxidative, antitumour, vasodilatory and antithrombotic properties of differing ginsenosides.<sup>14</sup>

There are over 250 species of aconite plants, many such as wolfsbane and devil's helmet have been known since ancient times to be poisonous. Their chief constituent is the alkaloid aconitine which activates voltage-sensitive sodium channels in skeletal muscle, cardiac and neuronal cells preventing repolarisation. Aconitine can be absorbed through skin or mucous membranes and causes spreading paraesthesia leading to respiratory paralysis and cardiac arrhythmias if ingested in doses as low as 1g of wild plant. Aconite when pharmacologically prepared contains minute doses of aconitine and its related alkaloids which are felt to increase cardiac output and treat supra-ventricular arrhythmias, although the effects in animal and human studies are highly variable, possibly reflecting the differing chemical makeup of the preparations studied.<sup>15</sup> In Eastern medicine uses of aconite tinctures include as cardiotonics, analgesics, anti-pyretics and aphrodisiacs.

An obvious issue with utilising this therapy in the West would be the need to gain regulatory approval for shenfu injection or its specific components. It is likely that this investigation may aid this process but there are issues both with its potential reproducibility and its application to other health-care systems. A significant omission is the lack of a placebo infusion in the control group, meaning bedside caregivers (and recovering patients) were not blinded as to the group allocation. This is difficult to justify as it inevitably raises the issue of conscious or unconscious bias in a myriad of other aspects of patient care which may have affected overall outcome. A number of reported secondary outcomes could be easily susceptible to bias - for example the increased MAP seen at 72 hours in the shenfu injection group was reported without noting the vasopressor dose administered. A lack of placebo has been a criticism of previous research in this area, with solutions such as sham acupuncture presumably more challenging than the yellow-coloured saline infusion this investigation could have utilised.<sup>11</sup>

The study also enrolled all suitable cardiac arrest patients consecutively before securing family consent, which was obtained in 97% of cases. Consecutive enrolment may reduce selection bias but requires careful oversight to ensure the retrospective consent process is comprehensive.<sup>16</sup> The power calculation assumed a baseline mortality of 70% but this is higher than expected for those who have achieved ROSC following cardiac arrest; under-powering may have been a confounding factor if the trial had not achieved a significant difference. In any event, the investigators continued recruitment to nearly double that planned. Whilst increasing study power, this is potentially problematic in that it may expose more patients than necessary to the non-beneficial arm of the investigation. These issues require effective oversight by the investigators, regulatory bodies and the publishing journal.

There is also no information provided on the median number of doses of shenfu injection received, the administration was planned for 14 days but the discussion notes that “a considerable proportion of patients were transferred out of the ICU within 1 week (many patients were unable to continue treatment in the ICU because of the high cost of hospitalization and many others abandoned treatment)”. It is difficult to confidently ascribe a treatment effect to the regime without firm evidence of its administration, raising further doubt over the internal validity of the study. It is possible also that baseline differences contributed to the study outcome; for example the median duration of cardiac arrest was 46% longer in the control group which may be a clinically if not statistically significant predictor of the worse outcome in this group.

Death following cardiac arrest often follows a withdrawal of life-sustaining therapies in the ICU. A strength of previous landmark research in this area has been a preset and rigorously followed algorithm for prognosticating and subsequent withdrawal of care.<sup>17</sup> There was no documented use of a similar protocol in this publication (including supplementary materials). As physician nihilism and early withdrawal has been highlighted as having a potential deleterious effect on survival post cardiac arrest this is especially concerning in an unblinded study where physician bias cannot easily be excluded.<sup>18</sup>

There is a further inconsistency in that the mean duration of mechanical ventilation and hospital stay are almost identical in both groups – typically one would expect a measurable gap between the two time-points. The corresponding standard deviations are also similar (and near-identical for the control group) suggesting a dissimilar distribution around a common mean is not a ready explanation. It may be that this was a mis-reporting of ICU length-of-stay: It is curious that neurological status (a key outcome in cardiac arrest trials) was assigned at ICU discharge but this time-point was seemingly not reported. As late improvement in status is a known phenomenon in hypoxic brain injury it also would have been preferable if this had been assessed at an equal and distant time-point in both groups. The Kaplan-Meier graphs presented do demonstrate that the significant mortality difference at day 28 did persist to 90 days, but longer term evidence of efficacy would be welcome.

There may be also differences in the patient population when compared to Western health-care systems. In-hospital cardiac arrest is less studied, and the outcome is generally reported to be much poorer than that in either group in this study, especially when considering that asystole was the presenting rhythm in over 80% of arrests.<sup>19</sup> It may be that in the West cardiac arrest occurs at a later stage after failure of appropriate management when recovery is unlikely; or in these Chinese centres patients may be more robust or post-arrest care more effective. This may reduce the magnitude of any

potential benefit to this therapy in the West. Some aspects of post-arrest care could be questioned: Therapeutic hypothermia was recommended but only utilised in 19% (although most centres have now moved towards Targeted Temperature Management (TTM) without induced hypothermia). The ventilatory targets were directed at avoiding extremes of oxygenation without specific mention of lung-protective ventilation (such as control of tidal volumes and inspiratory pressures). Dopamine is not a contemporary choice as vasopressor in Western critical care.

With these caveats in mind it is likely that shenfu injection (or selected components of it) would need to undergo progression through local phase 1-3 trials as well as regulatory approval to become an accepted therapy in Western critical care.

### **Where it sits in the body of the evidence**

This is the first published randomised controlled trial (RCT) evaluating shenfu injection following cardiac arrest in humans.

The UK National Cardiac Arrest Audit collected data from 188 UK hospitals and reported on in-hospital cardiac arrests occurring from April 2015 to March 2016.<sup>20</sup> There were 16,617 cardiac arrests included (1.3 per 1,000 hospital admissions). Median age was 76, 59% were male, 83.2% had been admitted medically. 57% of the arrests occurred in a ward, 10% in the Emergency Department, 5% in ICU and 10% in the coronary care unit. The presenting rhythm was PEA in 52%, VF/VT in 15% and asystole in 22%. Overall 50% of patients had a sustained ROSC and 20% survived to hospital discharge. Of the 3,655 patients with asystole as presenting rhythm 1,132 (31%) achieved ROSC of which 27% (309 patients, 8.7% overall) survived to hospital discharge.

In 2015 Mo published a meta-analysis of the effect of shenfu injection in 904 adults with septic shock. Twelve Chinese single-centre randomised controlled trials (RCTs) comparing shenfu injection against placebo were included, each with 49-120 participants. Pooled results suggested that shenfu injection raised MAP at one and six hours and reduced HR and serum lactate at six hours. Six of seven studies with mortality as an endpoint reported a significant mortality reduction with shenfu injection, but differing time-points made pooling data impossible. All studies were judged to be of poor methodological quality, of high risk of bias and with high heterogeneity in all pooled measurements ( $I^2 > 90\%$ ); limiting interpretation of the findings. Further RCTs were called for.

Wen-Ting et al in 2012 published a meta-analysis of the effect of shenfu injection in chronic and acute heart failure.<sup>21</sup> 97 RCTs were included, again all were of suboptimal methodological quality with no trial having adequate allocation concealment. On pooled

analysis shenfu injection was associated with an improvement in New York Heart Association heart failure classification of symptoms. Mortality was also reduced with shenfu injection, with pooled analysis of 11 studies comprising 978 patients, again with high heterogeneity ( $I^2=94\%$ ) and risk of bias.

### **Should we be reaching for shenfu injection following cardiac arrest?**

No - this is a single RCT with a high risk of bias undertaken in a population probably significantly different to those in Western ICUs. We should, however, welcome careful further study of this intriguing therapy.

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# Airway Trials





## MACMAN

**Lascarrou JB, Boisrame-Helms J, Bailly A, Le Thuaut A, Kamel T, Mercier E, et al. Video Laryngoscopy vs Direct Laryngoscopy on Successful First-Pass Orotacheal Intubation Among ICU Patients. A Randomized Clinical Trial. JAMA 2017;317(5):483-493**

### Introduction

Airway interventions are high risk procedures with the potential for catastrophe. This is magnified in a critical care setting, where the complexity of physiological derangement adds to any possible anatomical difficulty.<sup>1</sup> Therefore, it is understandable any technological advance which may make intubation easier would be vigorously pursued.

The development of video laryngoscopes has been impressive with a number of types available, divisible by blade type, as Macintosh type, angulated blade type and anatomically shaped blade with a guide channel.<sup>2</sup> As these devices all have different characteristics, it is easy to understand that proficiency with one does not guarantee proficiency with another, or with a conventional Macintosh. It has been consistently reported these devices provide a better view of the glottis, although this can fail to translate into improved first-pass intubation rates. In addition, video laryngoscopes can cause higher rates of laryngeal and pharyngeal trauma,<sup>3</sup> prolonged duration of intubation,<sup>4</sup> more severe hypoxaemia<sup>4</sup> and even higher mortality.<sup>5</sup> As much of the evidence for video laryngoscopes comes from the theatre setting, the use of these devices in the ICU remains largely unanswered, with just a few small trials available. It is against this background the McGrath Mac Videolaryngoscope Versus Macintosh Laryngoscope for Orotacheal Intubation in the Critical Care Unit (MACMAN) trial was performed.

### Synopsis

MACMAN was a multi-centre, open-label, randomised trial, undertaken in 7 French ICUs between May and December 2015, comparing the McGrath Mac videolaryngoscope with the Macintosh laryngoscope for orotracheal intubation in the intensive care unit. As both interventions were considered standard care, consent was not required, although information was provided to the patient or next of kin. All patients requiring intubation to facilitate invasive mechanical ventilation were eligible. Specific exclusion criteria included a contra-indication to orotracheal intubation, insufficient time to randomise, age less than 18 years, and pregnancy.

Randomisation was performed in blocks of 4 stratified by centre and level of expertise. An expert was considered to have worked in the ICU for at least 5 years, or at least 1 plus

2 years of anaesthesia experience. Training was provided in the use of both the Mac videolaryngoscope and conventional Macintosh laryngoscope. Both laryngoscopes had the same degree of angulation. Non-expert intubators were supervised by an expert intubator.

Both groups followed a protocol for intubation. Four methods of pre-oxygenation were permissible, each lasting  $\geq 3$  minutes, with the choice left to the physician's discretion: bag valve mask delivering 100% oxygen; a non-rebreathing mask delivering  $\geq 15$  L/min of oxygen; non-invasive ventilation using 100% oxygen; or high flow nasal oxygen at  $\geq 60$  L/min of 100% oxygen. General anaesthesia was induced with an anaesthetic agent and a neuromuscular blocker, with the choice again at the physician's discretion. Etomidate (0.2 - 0.3 mg/kg) or ketamine (1 - 2 mg/kg) were the preferred anaesthetic agents. Suxamethonium (1mg/kg) was the preferred neuromuscular blocker, although rocuronium (1 mg/kg) was also permissible. A stylet was not used on first attempt, as per French airway guidelines. Cricoid pressure was permissible but not stipulated. Adequacy of intubation was confirmed with end-tidal capnography over 4 breaths. For a failed first attempt, the same intubator could try a second time with the same laryngoscope or change to a second technique. During a second attempt with the MAC video laryngoscope, direct glottic visualisation was permissible.

370 patients were required to identify a 15% absolute increase in the primary outcome of first pass success, from 65% in the direct laryngoscopy group to 80% in the video laryngoscopy group, with 90% power, at a 5% significance level. Secondary outcomes were related either directly to the intubation process or to more general ICU parameters, and included the overall rate of successful intubation, time from induction of anaesthesia to confirmation of intubation, Cormack and Lehane grade of glottis view, rate of difficult intubation, requirement for alternative techniques, complications, including hypoxia and hypotension, duration of mechanical ventilation, lengths of ICU and hospital stay and 28-day mortality. A MACOCHA score was completed to assess predicted difficulty of intubation. Analysis was by the intention-to-treat principle, with a per-protocol analysis also undertaken. Those without data for the primary outcome were considered to have suffered a failed intubation.

489 patients were screened and 371 randomised, 186 to the video laryngoscopy group and 185 to the direct laryngoscopy group. Groups were largely equal at baseline, with the exceptions of there being more patients with acute circulatory failure in the video laryngoscopy group (n=32 vs. n=22; 17.2% vs. 11.9%), and also more patients with a grade 4 Mallampati score (n = 11 vs. n = 5; 9.9% vs. 4.7%). A typical patient was a male in his early 60s, with a BMI of 26, undergoing intubation for either neurological (~ 40%) or respiratory (~ 28%) failure, with a systolic blood pressure of 125 - 130 mm Hg, SpO<sub>2</sub> 95%

and a heart rate of just over 100/min. Non-expert intubators performed the first attempt in 83.8% of cases.

366 patients were successfully intubated. There was no difference between groups in the proportion of those intubated on first attempt; video laryngoscopy group, 67.7% vs direct laryngoscopy group, 70.3%; absolute difference, -2.5%; 95% CI, -11.9% to 6.9%;  $P = 0.60$ ). This finding was consistent when adjusted for operator expertise; failed first attempt with video laryngoscope (OR, 1.12; 95% CI, 0.71 to 1.78;  $P = 0.63$ ); and adjusted for MACOCHA (OR, 1.10; 95% CI, 0.69 to 1.75;  $P = 0.69$ ). The primary reason for failure to intubate differed between the 2 groups, being failure to access the glottis with the video laryngoscope (70% of failures) and inability to visualise the glottis with the direct laryngoscope (70% of failures). There was no difference in either the success rate of second attempts or total number of attempts (median of 1 in both groups). The median duration of intubation was equal at 3 minutes in both groups. A gum elastic bougie was used in 19% of cases in the video laryngoscope group and 13.8% in the direct laryngoscopy group. Numerically more patients suffered severe hypoxaemia in the video laryngoscope group (3.4% vs. 0.5%; absolute difference, 2.9%; 95% CI, -0.03 to 5.7;  $P = 0.06$ ). There were 4 cardiac arrests during intubation with the video laryngoscope in contrast to none in the other group. More patients in the video laryngoscopy group suffered severe life threatening complications (9.5% vs. 2.8%; absolute difference 6.7%; 95% CI, 1.8% to 11.6%;  $P = 0.01$ ). Expert intubators were more likely to achieve a successful first pass intubation (91.7% vs. 64.6%; absolute difference 27.1%; 95% CI, 18.2% to 35.8%;  $P = 0.001$ ). There was no difference in general ICU outcomes, including 28-day mortality of approximately 36% in both groups.

## Critique

MACMAN compared two forms of laryngoscopy, direct and video, in a largely non-expert group of intubators, in the difficult circumstances of physiological derangement in addition to the standard possibility of anatomical difficulties. The trial was well thought-out and administered. Selection criteria were sensible, randomisation was robust, groups were largely similar at baseline and the outcomes chosen were standard for laryngoscopy studies. However, despite all this, there were still some issues to grapple with.

Interestingly, issues of external validity raise questions about internal validity. A number of practices, some of which are unique to France, pose issues for those wishing to understand this trial. Firstly, the intubators appeared quite inexperienced. Whilst a figure of 50 to 60 prior supervised intubations may seem a lot, in reality, this is little over a week's worth of intubations in an ENT theatre, and is a figure a beginner in anaesthesia would likely acquire within his or her first 1 to 2 weeks. No-one would argue such a group

has achieved a significant level of competence. Such an effect is likely magnified when one considers these intubations were likely spread out over a period of time, or were possibly not in the recent past, thus preventing any consolidation of skills. Therefore, comparing two forms of laryngoscope in two groups of intubators, neither of whom may be overly proficient with either device, may not be optimal to allow any difference to be identified.<sup>6</sup> A pre-hospital study involving paramedics who also intubate infrequently, also published in 2017, too reported no difference in outcomes between the two forms of laryngoscopy.<sup>7</sup> It is compelling to see the near 50% increase in first pass success rate with experienced intubators in comparison with the inexperienced. Thus, did the trial simply lose power because those doing the majority of intubations were too inexperienced?

On a similar note, most airway competent clinicians would expect to be able to intubate the vast majority of Cormack-Lehane grade 1 to 2 patients, regardless of whether whether a video or direct laryngoscope was used. 90% of the video laryngoscope group and 80% of the direct laryngoscope group fell into this category, leaving approximately just 15% of the entire cohort of patients intubated as more anatomically difficult airways, and again potentially minimising the opportunity to see any real difference between the two approaches.

The McGrath Mac videolaryngoscope was an excellent comparator to the a conventional Macintosh laryngoscope, having the same degree of angulation, and thus standardising this aspect of laryngoscopy. However, by not using a gum elastic bougie or stylet on the first, as would be standard practice in many parts of the world if it were required, those using the video laryngoscope were placed at an immediate disadvantage. It is thus unsurprising the glottis was frequently seen but not catheterised. Another aspect of the trial which diverges from real-world practice is that those using the McGrath Mac videolaryngoscope were mandated to use it in its video mode for the first attempt. As a laryngoscope with the same geometric profile as a Macintosh, it is very easy to simply convert to a standard direct view during the same intubation attempt, an option the trial did not allow for.<sup>8</sup>

The increase in severe life threatening events seen with the video laryngoscope is puzzling to understand, given the presence of an expert airway provider supervising each procedure. Regardless of the laryngoscope used, once a patient's physiology becomes sufficiently deranged, they would be expected to intervene and rescue the situation. Why this response should differ depending on the laryngoscope used begs the question as to the experience of the supervisor. It is notable that length of time working in an ICU was one factor determining the level of a clinician's airway competence; it has been argued the exposure to, and performance of, intubations, should determine airway

competence, rather than the location of one's practice.<sup>8</sup> Perhaps the allure of a visible glottis proved too tantalising to the intubating team, including the supervising clinician, causing loss of situational awareness, and progressive physiological degradation during the apnoeic phase.

It is interesting to see 10% of the video laryngoscopy and 5% of the direct laryngoscopy view scored a Mallampatti grade 4 view pre-intubation. Many would consider such an airway to require intubation via an awake or sedated approach with a fibre-optic laryngoscope, although such an approach is not favoured in the very recent UK guidelines for the management of tracheal intubation in the critically ill adults.<sup>9</sup>

Regardless of the finer points of the trial, MACMAN adds to the growing body of evidence showing that video laryngoscopes improve the view of the glottis, but does not improve intubation rates. Before that is taken at face value, it is worth considering some confounders; firstly, expertise with a direct laryngoscope does not confer expertise with a video laryngoscope; secondly, as mentioned, video laryngoscopes would only realistically be expected to improve the possibility of intubation in Cormack and Lehane grade 3 and possibly grade 4 intubations, as viewed with a Macintosh laryngoscope; thirdly, this evidence largely pervades to inexperienced operators, rather than experienced clinicians. How relevant this is for anaesthetists who have performed hundreds and thousands of intubations is unclear. This point is especially pertinent in settings, such as the UK and Ireland, where the majority of intensivists are dual-trained anaesthetists, actively working in theatre.

Despite these critical points, MACMAN has many excellent virtues. It provides a robust demonstration that airway management, in this setting, using these devices and with intubators of this level of experience, provides similar rates of first pass success, with the caveat of a risk of more severe airway complications with the video laryngoscope. If your working environment mirrors that of this trial, then direct laryngoscopy certainly is not inferior. However, if this does not accurately reflect who intubates in your ICU, or how they do it, then the question of video laryngoscopy or direct laryngoscopy may remain unanswered for a little longer.

### **Where this sits in the body of evidence**

Silverberg and colleagues undertook a single centre, randomised controlled trial comparing video laryngoscopy (GlideScope) with direct laryngoscopy in 117 ICU patients requiring intubation.<sup>10</sup> Groups were similar at baseline. The GlideScope was associated with a higher first-attempt success rate (74% vs.40%;  $P < 0.01$ ), faster time to intubation (120 s vs. 218 s; ( $P < 0.01$ ) and lower number of attempts to achieve intubation (1.39 vs.

1.93;  $P < 0.01$ ). The glottic view was also improved with the video laryngoscope. There were no between-group differences in rate of complications.

The single centre FELLOW trial (Facilitating Endotracheal intubation by Laryngoscopy technique and apneic Oxygenation Within the ICU) randomised 150 critically ill patients to intubation with either a video laryngoscope (McGrath videolaryngoscope, GlideScope or Olympic Video Bronchoscope) or direct laryngoscopy (curved MacIntosh or straight Miller laryngoscopes). Intubation was performed by pulmonary and critical care fellows, supervised by an attending, who could give feedback during the procedure. There was no difference in the primary outcome of first-attempt success rate (video laryngoscopy 68.9% vs. direct laryngoscopy, 65.8%;  $P = 0.68$ ). There was no difference in any secondary outcomes

The Canadian Critical Care Trials Group completed a small pilot ( $n = 40$ ) randomised controlled trial comparing direct with video laryngoscopy in novice intubators. Of note, the trial excluded hypoxic or hypotensive patients, and those with an anticipated difficult airway.<sup>11</sup> The intubators were non-anaesthetists and had received 1 hour of teaching and training on mannequins. Patients were similar in the two groups, and mainly received intubation for respiratory failure, and mostly had a Mallampati score of 1 or 2. The majority of intubations were performed in the ICU. There was no difference in the number of intubation attempts required, or any other parameter recorded, other than video laryngoscopes resulting in better visualisation of the glottis (Cormack & Lehane grade 1; video laryngoscopy group 85% vs. direct laryngoscopy group, 30%;  $P < 0.001$ ) but a greater first-attempt failure rate (42% vs. 5%;  $P = 0.03$ ).

Ducharme undertook a pilot randomised controlled trial amongst paramedics who infrequently intubate, comparing video (King Video Laryngoscope) with direct laryngoscopy in 82 patients, mostly suffering out-of-hospital cardiac arrest.<sup>7</sup> There was no difference in rates of first-attempt success (video laryngoscopy, 62.5% vs. direct laryngoscopy, 66.7%) or overall success (72% vs. 81%;  $P = 0.37$ ).

Huang performed a 2017 systematic review and meta analysis, including 5 trials ( $n = 1,301$ ), comparing video with direct laryngoscopy for emergency intubation in the ICU.<sup>12</sup> There was no difference in first-attempt success rate (RR, 1.08; 95% CI, 0.92 to 1.26;  $P = 0.35$ , time to intubation (mean difference, 4.12 s; 95% CI, -15.86 to 24.09;  $P = 0.69$ ), difficult intubation (RR, 0.72; 95% CI, 0.30 to 1.70;  $P = 0.45$ ) or mortality (RR, 1.02; 95% CI, 0.84 to 1.25;  $P = 0.83$ ). Video laryngoscopy was associated with improved glottic visualisation (RR, 1.24; 95% CI, 1.07 to 1.43;  $P = 0.003$ ).

Jiang and colleagues completed a recent systematic review and meta analysis, including 12 randomised controlled trials totalling 2,583 patients, comparing video and direct laryngoscopy for intubation in emergency and critically ill patients.<sup>13</sup> Low quality evidence suggested no increase in first-attempt success rate with the video laryngoscope (12 studies; RR, 0.93; 95% CI, 0.82 to 1.06; P = 0.28), although there was significant heterogeneity amongst studies ( $I^2 = 91\%$ ). In the pre-hospital setting, video laryngoscopes were associated with a worse first pass success rates (3 studies; n = 647; RR, 0.57; P < 0.01; high-quality evidence) but there was no difference in the in-hospital setting (nine studies; n = 1,936; RR, 1.06; ; P = 0.14; moderate-quality evidence).

A UK guideline<sup>9</sup> on intubation in the critically ill, prepared jointly by the Difficult Airway Society, Faculty of Intensive Care Medicine and Royal College of Anaesthetists, which comments on the use of video laryngoscopes, suggests (1) intubators should be trained in their use, (2) their use should be considered first line in anticipated difficult intubations (MACOCHA score  $\geq 3$ ), (3) if a poor glottic view is encountered with a video laryngoscope, a hyperangulated blade prolongs easy intubations, and (4) awake video laryngoscopy may be considered by those with the appropriate skills in patients with an anticipated difficult airway.

### **Should we disregard video laryngoscopes in the ICU.**

Not just yet. MACMAN adds to the evidence-base suggesting little benefit from video laryngoscopy over direct laryngoscopy, although there are issues with external generalisability.

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# Respiratory Trials



## ART

**Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs. Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome. A Randomized Clinical Trial. JAMA 2017;318(14):1335-1345**

### Introduction

The acute respiratory distress syndrome (ARDS) is a condition characterised by collapsed and consolidated lung, typically in the basal lung portions, contributing to shunt and hypoxia. Recruitment maneuvers, which transiently increase transpulmonary pressure, are used to reinflate these areas of the lung, which are subsequently maintained open by the application of high levels of positive end-expiratory pressure (PEEP). This strategy has broadly been termed the open lung approach and has been tested in various forms in several randomised controlled trials reporting patient-centred outcomes.<sup>1-4</sup> While there is reasonable evidence to construct a contemporary paradigm of protective ventilation, consisting of a tidal volume of 6 ml/kg, maintenance of a plateau pressure of < 30 cm H<sub>2</sub>O, and the use of PEEP, probably at a higher level in more severe hypoxaemia, the evidence for the open lung approach is less clear.

Whether recruitment maneuvers, which expose the lung to extremely high transpulmonary pressure, are efficacious, given their propensity to cause both barotrauma and circulatory depression, is uncertain.<sup>5</sup> Similarly, the level at which PEEP should be set remains unclear. Compounding these uncertainties in the open lung approach are the methods by which recruitment manoeuvres should be administered and how the optimal PEEP value should be both chosen and delivered. Finally, the biological hypothesis that opening the injured lung is beneficial is not above questioning, as perhaps the exudative injury filling the lung with inflammatory fluid is protective and allows damaged alveoli time to repair unexposed to potentially harmful ventilation or levels of oxygen.

### Synopsis

The Alveolar Recruitment for ARDS Trial (ART) was an open label, randomized controlled trial, undertaken in 120 ICUs from nine countries between 2011 and 2017, comparing a strategy of recruitment maneuvers combined with PEEP adjusted to the optimal respiratory system compliance, with a low-PEEP strategy, in patients with moderate-to-severe ARDS receiving invasive mechanical ventilation for less than 72 hours. Eligible patients were assessed in a two-step process – screening and confirmation. Screening consisted of meeting inclusion, notably meeting the old American-European Consensus

Conference criteria for ARDS, and avoiding the exclusion criteria, which were cognisant of the haemodynamic effects of high airway pressures, namely escalating vasopressor requirements and a mean arterial pressure less than 65 mm Hg, as well as any contraindication to hypercapnoea. In the confirmatory enrichment phase, to ensure patients most likely to have severe, persistent ARDS were recruited, all potential patients were subjected to a standardised three hour period of ventilation using low PEEP and low tidal volume, followed by 30 minutes of ventilation with an  $\text{FiO}_2$  1.0 and  $\text{PEEP} \geq 10$  cm  $\text{H}_2\text{O}$ . If the  $\text{PaO}_2/\text{FiO}_2$  was less than 26.6 kPa after this time, the patient was enrolled into the trial.

Randomisation occurred in a 1:1 fashion via a web-based system, in blocks of four, stratified by site, age (above or below 55 years) and  $\text{PaO}_2/\text{FiO}_2$  (above or below 100 mm Hg). Control patients were ventilated as per the ARMA trial low tidal volume group – 6 ml/kg predicted body weight, plateau pressures < 30 cm  $\text{H}_2\text{O}$  and PEEP set by the ARDSnet PEEP/ $\text{FiO}_2$  table.<sup>13</sup> The ventilatory strategy of the intervention group is described in figure 1. Midway through the trial, following three episodes of cardiac arrest possibly associated with the recruitment maneuvers, the intervention was modified (Figure 1).

The primary outcome was 28-day mortality, with secondary outcomes including lengths of ICU and hospital stay, ventilator-free days, likely ventilator-induced barotrauma within 7 days (pneumothorax requiring drainage, pneumomediastinum, subcutaneous emphysema or pneumatocele > 2 cm on imaging), and mortality within ICU, within hospital and at 6 months.

ART was an event-driven trial, with 520 events (deaths by 28 days) required to provide 90% power, at a 5% significance level, to identify a hazard ratio of 0.75. Analysis was performed on an intention-to-treat basis and hypothesis tests were two sided. Secondary outcomes were not corrected for multiple hypothesis testing and were considered to be exploratory. Pre-specified subgroups consisted of  $\text{PaO}_2/\text{FiO}_2$  (above or below 100 mm Hg), SAPS 3 score (above or below 50), pulmonary vs. extra-pulmonary cause of ARDS, duration of ARDS ( $\leq 36$  hours vs. 36 to 72 hours), mechanical ventilation ( $\leq 2$  days, 3-4 days,  $\geq 5$  days) and prone position.

2,077 patients were screened and 1,013 recruited, with 501 allocated to the recruitment maneuver / high PEEP intervention group and 512 to the low PEEP control group. The main reasons for non-recruitment were meeting exclusion criteria (81%), including inadequate hypoxaemia after standardised ventilation, and hypotension, plus other criteria, mainly a lack of consent. Three patient representatives withdrew consent, and 23 were censored for follow up at between 2 and 6 months, leaving 1,010 patients

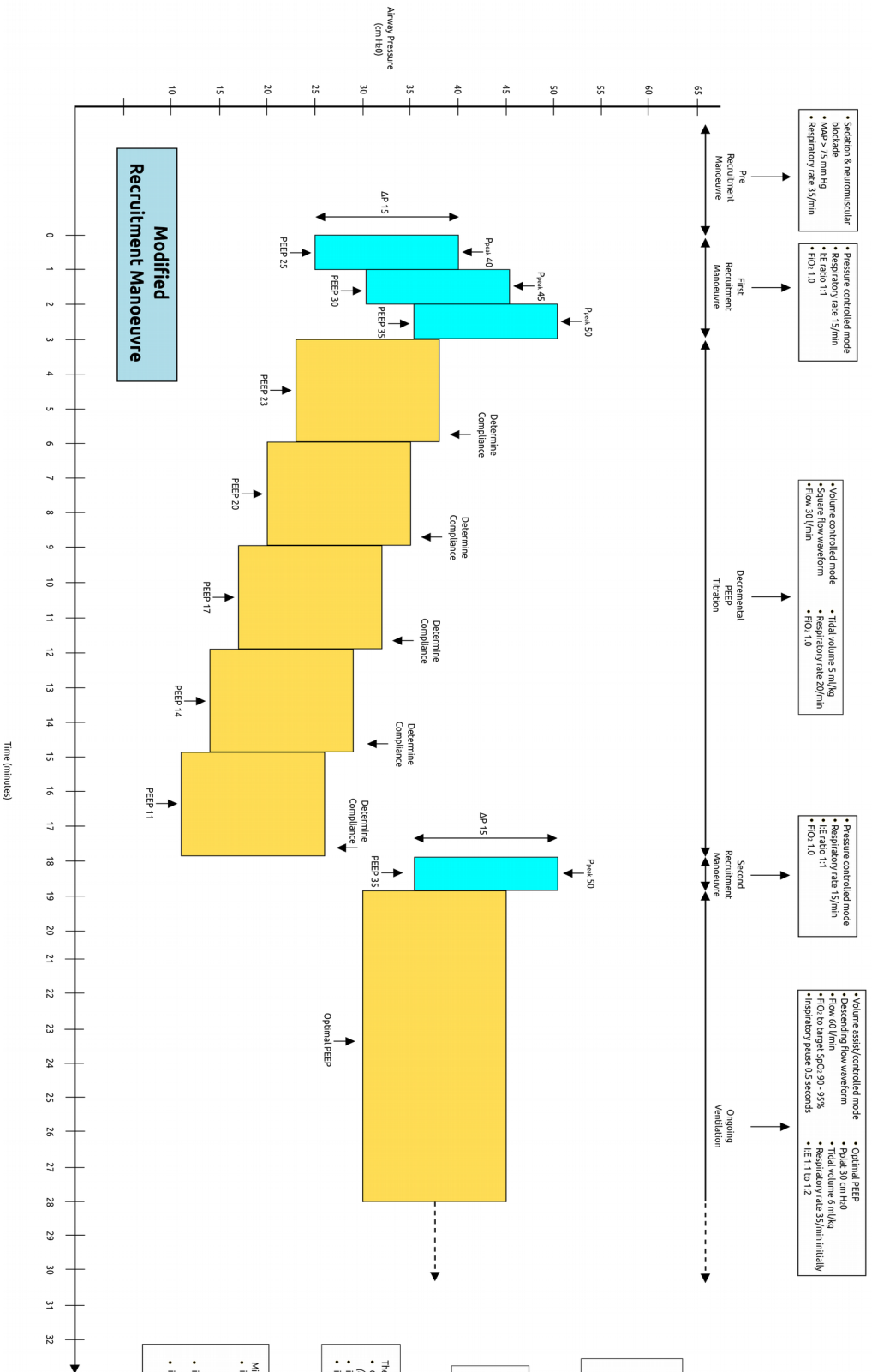


Figure 1. The ART trial intervention

**Notes**

**Recruitment Manoeuvre Termination**

The maximum alveolar recruitment manoeuvre should be terminated if:

- heart rate > 150 bpm or < 60 bpm
- oxygen saturation < 90% for > 2 minutes
- reduction of systolic arterial pressure to < 50 mm Hg
- reduction of SpO<sub>2</sub> to < 88% for > 30 seconds
- severe heart arrhythmias
- other reason as determined by the treating medical team

**Static Compliance**

Static compliance =  $\frac{\text{Tidal volume}}{P_{\text{max}} - \text{PEEP}}$   
*(with P<sub>max</sub> measured using a 2 second respiratory pause)*

- Optimal PEEP = PEEP value at maximum compliance plus 2 cm H<sub>2</sub>O

**Recruitment Manoeuvre Repetition**

The maximum alveolar recruitment manoeuvre (i.e. first RM) could be repeated:

- once per 24 hours if the first RM was successful
- if a rise in P<sub>a</sub>O<sub>2</sub> / H<sub>2</sub>O<sub>2</sub> of > 50 mm Hg
- if P<sub>a</sub>O<sub>2</sub> < 250 mm Hg and there was a decrease in P<sub>a</sub>O<sub>2</sub> / H<sub>2</sub>O<sub>2</sub> of > 50 mm Hg
- if there was a ventilator disconnect with PEEP ≥ 12 cm H<sub>2</sub>O

**Recruitment Manoeuvre Modifications**

Midway through the trial the recruitment manoeuvre was modified:

- In the first recruitment manoeuvre, the PEEP in each period was altered
  - (1) 25 cm H<sub>2</sub>O x 1 minute → 25 cm H<sub>2</sub>O x 1 minute
  - (2) 25 cm H<sub>2</sub>O x 1 minute → 25 cm H<sub>2</sub>O x 1 minute
  - (3) 25 cm H<sub>2</sub>O x 1 minute → 35 cm H<sub>2</sub>O x 1 minute
  - (4) 35 cm H<sub>2</sub>O x 1 minute → 35 cm H<sub>2</sub>O x 1 minute
- In the decremental PEEP trial, each interval was reduced from 4 minutes to 3
- In the second recruitment manoeuvre PEEP was reduced
  - 45 cm H<sub>2</sub>O x 2 minutes → 35 cm H<sub>2</sub>O x 1 minute

evaluable for the primary outcome (intervention group, 501 patients and control group, 509 patients).

95.8% of the intervention group received a recruitment maneuver; 2% did not due to hypotension, pneumothorax or other reason. The mean (SD) titrated PEEP was 16.8 (3.8) cm H<sub>2</sub>O. Most (78.4%) of the intervention group had a subsequent recruitment maneuver after PEEP titration, although 62.7% did not undergo a further recruitment maneuver within the first week. Groups separated well in terms of respiratory parameters (Table 8). There was no difference in the requirement for rescue therapies for hypoxaemia.

	Day 1			Day 3			Day 7		
	Intervention	Control	P Value	Intervention	Control	P Value	Intervention	Control	P Value
<b>Vt</b>	5.6	5.7	0.006	5.8	5.8	0.20	6.1	6.2	0.67
<b>PEEP</b>	16.2	12.0	<0.001	14.2	10.5	<0.001	11.6	9.6	<0.001
<b>Pplat</b>	27.9	25.4	<0.001	26.3	24.0	<0.001	24.1	23.2	0.05
<b>ΔP</b>	11.7	13.5	<0.001	12.1	13.5	<0.001	12.5	13.6	0.001
<b>Cstat</b>	32.8	29.7	0.001	34.0	31.3	0.06	34.5	32.4	0.14
<b>RR</b>	30.4	29.1	0.001	29.2	28.0	0.003	25.9	26.4	0.43
<b>P/F</b>	221.9	164.7	<0.001	241.4	184.2	<0.001	262.7	215.1	<0.001

**Table 8. Respiratory parameters**

*Vt* = tidal volume, *PEEP* = positive end expiratory pressure, *Pplat* = plateau pressure,  $\Delta P$  = driving pressure, *Cstat* = static compliance, *RR* = respiratory rate, *P/F* = PaO<sub>2</sub>/FiO<sub>2</sub>

There was a significantly increased 28-day mortality in the intervention group (55.3% vs. 49.3%; HR, 1.20; 95% CI, 1.01 to 1.42; P = 0.041). This persisted at 6 months (65.3% vs. 59.9%; HR, 1.18; 95% CI, 1.01 to 1.38; P = 0.04) and was consistent across sensitivity analyses. Although there was no difference in refractory hypoxaemia, the interventional group suffered more barotrauma {5.6% vs. 1.6%; risk difference (RD), 4.0; 95% CI, 1.5 to 6.5; P = 0.001}, had more pneumothoraces requiring drainage (3.2% vs. 1.2%; RD 2.0; 95% CI 0.2 to 3.8; P = 0.03) and had a higher mortality rate within the first 7 days. Despite this, there were no differences in ICU (60.6% vs. 55.8%; RD, 4.8; 95% CI, -1.5 to 11.1; P = 0.13) or hospital mortality (63.8 vs. 59.3; RD, 4.5; 95% CI, -1.7 to 10.7; P = 0.15). The intervention also resulted in less ventilator-free days at day 28 (5.3 vs. 6.4; mean difference -1.1; 95% CI -2.1 to -0.1; P=0.03). Exploratory analyses investigating the modes of deaths suggested more patients in the intervention group died within 7 days with barotrauma (7 patients vs. 0 patients) and also either developed new hypotension, required new vasopressors or an increase in vasopressors within 1 hour of the intervention. Interestingly, there was no difference in the rates of death with severe acidaemia, refractory hypoxaemia or cardiac arrest on day 1. No subgroup effects were seen.

## Critique

This was an excellent, robust trial which provides compelling evidence of the harms of a ventilatory strategy using aggressive recruitment maneuvers combined with high PEEP in patients with moderate-to-severe ARDS. For those using such an approach, this large international trial demands a rethink of this practice.

ART has many strengths, including having high internal validity, with a well designed and described protocol which achieved separation between groups in ventilatory practice, and good external validity, with 120 recruiting centres in 9 countries from 3 continents. The clear signal of harm is unequivocal, coherent at different time-points across the trial, and appears related to a combination of barotrauma and circulatory dysfunction. It is noteworthy that the Canadian high frequency oscillatory ventilation trial OSCILLATE, which similarly subjected patients to high airway pressures, also reported increased mortality, which was likely to be due, at least partly, to circulatory embarrassment. Another issue highlighted in OSCILLATE was the excessive requirement for sedation in the oscillation group. Although excessive sedation may contribute to the adverse outcomes in other critical care trials,<sup>6,7</sup> there was no signal of such an influence in ART.

Amongst many talking points, one topical matter stands out in particular, especially as some of the ART investigators highlighted this previously. A 2015 retrospective analysis of nine trials investigating protective ventilation in ARDS noted an association between driving pressure, which is the difference between PEEP and plateau pressures, and outcome, with higher driving pressures being linked to higher mortality.<sup>8</sup> Indeed, all the beneficial effects of protective ventilation, such as low tidal volume, were statistically determined to be mediated through reduction in driving pressure. In the ART trial, despite having significantly higher driving pressures, the control group had better outcomes, calling into question this the validity of this parameter as an outcome predictor or modifier. Future prospective randomised trials will be required to address this question more fully.

Viewing the outcomes uncritically, an apparent disconnect is seen between discharge and time-point mortality rates. The lack of mortality effect at discharge from ICU and hospital merely reflects the in-built biases in endpoints reliant on subjective discharge planning. This is lost using objective time points. No signal of benefit was reported in any outcome, including all strata and subgroups, implying the interventional strategy is uniformly without benefit when applied to the intervention group as a whole.

The trial does have limitations. The very high PEEP used in the recruitment maneuvers may be unfamiliar to many, with the, now justified, fear of cardiovascular collapse an impediment to widespread adoption. However, this trial has clearly answered this

question, that such recruitment maneuvers are overall detrimental, when applied in such a systematic way. While it may be logical to consider such a ventilatory strategy in the most hypoxic ARDS patients, a deeper analysis of outcomes based on hypoxia quartiles fails to identify benefit even in the most hypoxaemic patients.

This leads to the subject of personalised medicine, a pertinent issue in a syndrome like ARDS, where the broad definition encapsulates a very heterogenous group of patients, with conditions as disparate as pneumonia, atelectasis, pulmonary malignancy and pulmonary fibrosis.<sup>9</sup> The enrichment period prior to recruitment, using standardised ventilatory settings designed to identify and exclude patients with transient hypoxia is laudable, and attempts to remove the low risk group of patients with transient ARDS who have a much superior outcome than those with ARDS persisting beyond 24 hours.<sup>10</sup> Again such an approach appears effective in selecting a cohort of patients where it is possible to determine an effect from an intervention.<sup>11</sup> This is important in a condition criticised for being so heterogenous many investigated therapies have little hope of establishing efficacy.<sup>10</sup>

A second potential criticism surrounds the use of oxygenation to determine best PEEP. While such an approach is relatively easy to implement, it is unclear if this should be the chosen method of setting PEEP. Multiple alternatives exist,<sup>12</sup> including using CT to visualise the percentage increase in lung aeration following lung recruitment, electrical impedance, ventilatory waveforms, such as identifying the lower inflection point on a pressure / volume curve, and transpulmonary pressure. The ARMA trial, comparing 6 ml/kg predicted body weight tidal volume in association with plateau pressures less than 30 cm H<sub>2</sub>O with a combination of 12 ml/kg and 50 cm H<sub>2</sub>O reported improved oxygenation in the high tidal volume/plateau pressure group at 24 hours.<sup>13</sup> Ultimately, this resulted in a 9% absolute mortality increase, highlighting the potential weaknesses of oxygenation-focused mechanical ventilation.

The choice of a stepwise PEEP recruitment method, rather than sustained inflations, typically a static airway pressure of 40 cm H<sub>2</sub>O for 40 seconds, or sighs, intermittent elevations of tidal volumes and transpulmonary pressures, deserves comment. Little outcome evidence exists for any of these choices.<sup>5</sup> By choosing a more aggressive recruitment maneuver, using very high airway pressures, briefly as high as 50 cm H<sub>2</sub>O, and lasting 20 to 26 minutes, the trialists delivered a definite physiological effect, as exemplified by between-group differences in mean airway pressure. However, it is instructive to see just 40% of patients in the interventional arm completed the stepwise escalating PEEP increase up to 45 cm H<sub>2</sub>O. Regardless of the manner in which individual clinicians undertake recruit maneuvers, and the similarity, or otherwise, of the approach in ART, there is now excellent evidence against the use of this protocol, and an

unambiguous caution against recruitment maneuvers as a systematic approach to patients with moderate-to-severe ARDS.

It is interesting to see the low implementation of proning, at just 10% in each group. As a safe, cheap intervention, with a large mortality benefit,<sup>16</sup> it is unclear why this should be the case, and somewhat limits the external generalisability of the trial to centres which prone more frequently. However, in the large global LUNG-SAFE observational study,<sup>17</sup> proning was used in 16% of those with severe ARDS, a finding consistent with the practice observed in ART.

Overall, this is an excellent trial which clearly advances the science of conventional mechanical ventilation and strongly reinforces the evidence that ventilator-induced injury very much exists. Given few patients with ARDS appear to die from refractory hypoxaemia, perhaps a change in approach away from aggressive ventilation, to either permissive respiratory failure, or ultra-protective ventilation, using extra-corporeal CO<sub>2</sub> removal, as is being investigated in numerous studies, including the 1,200 patient REST trial,<sup>14</sup> should now be the focus of future investigations.

### **Where this sits in the body of evidence**

Earlier in 2017, Leme and colleagues published a Brazilian single centre, randomised controlled trial comparing strategies of intensive alveolar recruitment with moderate alveolar recruitment in 320 hypoxaemic patients post cardiac surgery who were receiving low tidal volume ventilation (*this trial is described in detailed in the next chapter*).<sup>19</sup> The intensive recruitment group received 3 x 1 minute periods of PEEP at 30 cm H<sub>2</sub>O, with a driving pressure of 15 cm H<sub>2</sub>O, intervened with 1 minute periods of PEEP of 13 cm H<sub>2</sub>O. Following this, PEEP was maintained at 13 cm H<sub>2</sub>O. The moderate recruitment group received 3 x 0.5 minute periods of CPAP at 20 cm H<sub>2</sub>O, with 1 minute intervals with a PEEP of 8 cm H<sub>2</sub>O. PEEP was maintained at 8 cm H<sub>2</sub>O after the recruitment period. Both groups underwent a second recruitment period 4 hours later. The post-operative pulmonary complication score, the primary outcome for the trial, was significantly reduced with intense alveolar recruitment; mean, 1.8; 95% CI, 1.7 to 2.0; vs. 2.1; 95% CI, 2.0 to 2.3; common OR 1.86; 95% CI, 1.22 to 2.83; P = 0.003. In contrast to the intervention group in the ART trial, patients in the intense recruitment group were subjected to a similar PEEP of 30 cm H<sub>2</sub>O, although for a total of just 3 minute only, and without a subsequent decremental PEEP trial, in comparison to a total of 20 to 26 minutes in the ART trial.

In 2008/2009, Hodgson and colleagues performed a short-term, small, single centre randomised controlled trial in 20 patients with ARDS, comparing an open lung strategy with a conventional ARDSnet protective ventilation approach.<sup>3</sup> The open lung strategy



consisted of using a tidal volume less than 6 ml/kg, low airway pressures, permissive hypercapnoea, a staircase recruitment manoeuvre and high PEEP. The ARDSnet protective ventilation approach<sup>13</sup> used 6 ml/kg tidal volume with plateau pressure less than 30 cm H<sub>2</sub>O. The two groups were similar at baseline, maintained comparable ventilatory parameters over the first 24 hour study period, but with the exception of PEEP (approx 15 – 17 cm H<sub>2</sub>O in the interventional group vs. 10 – 11 cm H<sub>2</sub>O in the control group). The interventional group had lower plasma IL-8 and TNF- $\alpha$  levels, and improved PaO<sub>2</sub>/FiO<sub>2</sub> and static lung compliance. Patient-centred outcomes were similar, although this trial was not powered for these outcomes.

This pilot study has led to the large international PHARLAP (**P**ermissive **H**ypercapnia, **A**veolar **R**ecruitment, **L**ow **A**irway **P**ressures, NCT01667146) from the same investigators. Due to the results of the ART trial, PHARLAP ceased recruiting in mid October 2017 on safety grounds. Results are due sometime in 2018.

Kacmarek and colleagues undertook a randomised controlled trial comparing an open lung approach with the conventional ARDSnet protective ventilation strategy in 200 patients with ARDS.<sup>15</sup> This was the first trial in this field to use an enrichment strategy. All patients, who were between 12 and 36 hours after the onset of ARDS, were subjected to a standardised period of ventilation, including  $\geq$  PEEP 10 cm H<sub>2</sub>O, to ensure a cohort likely to benefit from an open lung approach were recruited. Those with a PaO<sub>2</sub>/FiO<sub>2</sub>  $\leq$  200 mm Hg were included and randomised. The open lung group received recruitment maneuvers followed by a decremental PEEP trial, identifying optimal PEEP based on dynamic lung compliance. For the recruitment maneuvers, a peak pressure of 50 to 60 cm H<sub>2</sub>O was used, in association with a PEEP of 35 cm H<sub>2</sub>O. Each patient in the intervention group received an average of 2.5 recruitment maneuvers. The control group did not receive recruitment maneuvers and had PEEP adjusted as per the ARDSnet FiO<sub>2</sub>-PEEP table. The trial was terminated early for poor recruitment, after 200 of a planned 600 patients were enrolled over 6 years. Groups were similar at baseline. Ventilatory parameters separated well between the two groups, with the open lung group having higher PEEP, lower driving pressure and lower FiO<sub>2</sub>. There was no difference in major adverse events. Despite ventilatory improvements, but in the setting of an underpowered trial, there was no difference in the primary outcome of 60-day mortality (open lung 28% vs. ARDSnet 33%) or other patient-centred outcomes.

Meade and colleagues performed a multi-centre randomised controlled trial in 983 consecutive patients with ARDS in 30 ICUs from 3 countries, investigating an open lung approach including recruitment maneuvers, higher PEEP and plateau pressures  $\leq$  40 cm H<sub>2</sub>O.<sup>2</sup> All patients were ventilated at 6 ml/kg predicted body weight. PEEP was adjusted according to the ARDSnet PEEP-FiO<sub>2</sub> table, which was modified for the higher PEEP

group. The intervention group received a recruitment maneuver at the beginning of the trial and after each ventilator disconnect, up to 4 times per day. Groups were similar at baseline and separated in terms of PEEP (approx 15 vs. 10 on day 1, 12 vs. 9 on day 3 and 10 vs. 8 cm H<sub>2</sub>O on day 7), FiO<sub>2</sub> (the intervention group was received approximately 10% less oxygen at each timepoint) and PaO<sub>2</sub> / FiO<sub>2</sub>. There was no difference in the primary outcome of all-cause hospital mortality (intervention group, 36.4% vs. control group, 40.4%; RR, 0.90; 95% CI, 0.77 to 1.05; P = 0.19) or secondary outcome of barotrauma (11.2% vs. 9.1%, respectively.) The intervention group did have significantly lower rates of refractory hypoxemia (4.6% vs. 10.2%), death with refractory hypoxemia (4.2% vs. 8.9%), and use of rescue therapies (5.1% vs. 9.3%).

Amato and colleagues completed a small, single centre randomised controlled trial in 53 patients with early ARDS, comparing a control group, ventilated high Vt (12 ml/kg IBW) with lowest acceptable PEEP, with an interventional group, ventilated using PEEP set above the lower inflection point on the static pressure–volume curve, tidal volumes of <6 ml/kg, driving pressures < 20 cm H<sub>2</sub>O above the PEEP value, permissive hypercapnia and frequent recruitment maneuvers, using CPAP of 35 to 40 cm H<sub>2</sub>O for 40 seconds.<sup>1</sup> Groups were similar at baseline and separated well in terms of ventilatory settings. The study was stopped after the fifth interim analysis after a significant difference in 28-day mortality was seen, in favour of the interventional strategy (38% vs. 71%, P<0.001).

A very recently published systematic review and meta analysis, incorporating 8 randomised controlled trials and 2,728 patients, compared higher versus lower PEEP in patients with ARDS.<sup>4</sup> Mean PEEPs were 15.1 ± 3.6 cm H<sub>2</sub>O and 9.1 ± 2.7 cm H<sub>2</sub>O, in the higher and lower PEEP groups, respectively. In 6 trials, totalling 2,580 patients (2 trials which did use a low tidal volume strategy in the low PEEP group were excluded), there was no significant difference in 28-day mortality (higher vs. lower PEEP; RR 0.91, 95% CI, 0.80 to 1.03), barotrauma, new organ failure, or ventilator-free days. A secondary analysis including all eight trials and 2,728 patients reported a significant mortality reduction for high PEEP strategies (RR, 0.84; 95% CI 0.71 to 0.99). No effect was seen when stratified for either recruitment maneuvers or method of setting PEEP (physiological targets or PEEP/FiO<sub>2</sub> table)

Lu and colleagues pooled 9 multi-centre and 6 single centre randomised controlled trials investigating the open lung approach in 3,134 patients with ARDS and found this approach significantly reduced hospital mortality (RR, 0.88; 95% CI, 0.80 to 0.97; P = 0.009), 28-day mortality (RR, 0.83; 95% CI, 0.71 to 0.96; P = 0.010) and ICU mortality (RR, 0.77; 95% CI, 0.65 to 0.92; P = 0.003).<sup>16</sup> Of the 4 studies testing recruitment maneuvers in association with high PEEP and reporting mortality, there was a significant mortality

reduction with this open lung approach (36.2% vs. 41.2%; RR, 0.87; 95% CI, 0.76 to 0.99; P = 0.04).

**Should we routinely use recruitment maneuvers and titrated PEEP, as described in the ART trial, in patients with moderate-to-severe ARDS?**

No. The open lung approach, as described in the ART trial, is harmful and should not be used.

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## Post-Operative Alveolar Recruitment

**Leme AC, Hajjar LA, Volpe MS, Fukushima JT, Santiago RR, Osawa EA et al. Effect of Intensive vs. Moderate Alveolar Recruitment Strategies Added to Lung-Protective Ventilation on Postoperative Pulmonary Complications. A Randomised Clinical Trial. JAMA 2017;317(14):1422-1432**

### Introduction

Postoperative pulmonary complications (PPCs) incorporate a wide variety of pathological processes and can range from an innocuous increase in sputum production to a life threatening pneumothorax or re-intubation for respiratory failure. Definitions of PPCs vary, and this lack of specificity has resulted in a wide variation in the quoted frequency of PPCs (20 - 30% of those undergoing non-cardiac surgery and 19 - 59% post-thoracic surgery).<sup>1-3</sup> PPCs can lead not only to increased length of ICU and hospital stay but an increase in perioperative morbidity and mortality. One epidemiological study found surgical patients who developed a PPC had a 30 day mortality of 18.5% compared to 2.5% for those who did not.<sup>4</sup>

The development of PPCs depends on patient-related risk factors, some of which are modifiable, such as smoking and obesity. Surgical factors are also important, for example, cardiac and thoracic surgical procedures appear to be at particularly high risk. Recent studies have examined how a particular intra-operative ventilatory strategy may affect the development of PPCs.<sup>5,6</sup> A non-protective ventilatory strategy can predispose a previously normal lung to injury through atelectrauma, volutrauma and barotrauma. A small single centre study of 69 cardiac surgical patients ventilated with a low tidal volume (Vt) and undergoing alveolar recruitment maneuvers demonstrated a reduction in inflammation and improvement in lung mechanics.<sup>7</sup> The effect of perioperative alveolar recruitment maneuvers, in patients receiving low Vt ventilation, on clinically relevant, patient-centred outcomes remains unknown.

### Synopsis

This single centred, non-blinded, randomised controlled trial recruited postoperative patients admitted to a cardiac surgical intensive care unit in Brazil. The investigators hypothesized an intensive alveolar recruitment strategy, in addition to lung protective ventilation, would reduce PPCs in this particular patient cohort.

Elective cardiac surgical patients were eligible for randomisation if they had a PaO<sub>2</sub>:FiO<sub>2</sub> ≤ 250 mm Hg with a PEEP ≥ 5 cmH<sub>2</sub>O on admission to the ICU. Among the exclusion criteria were emergency cases, those with an ejection fraction of < 35%, patients with

documented obstructive lung disease and those requiring noradrenaline at a dose of  $\geq 2$   $\mu\text{g}/\text{kg}/\text{min}$ .

The primary outcome measure was the severity of PPCs during the hospital stay, as measured on an ordinal scale of 0 – 5 (Table 9). Secondary outcomes included length of ICU and hospital stay as well as hospital mortality and incidence of barotrauma.

Post-Operative Pulmonary Complication Score		
0	No Symptoms	Minor
1	Dry cough/ abnormal lung findings with temperature $> 37.5^{\circ}\text{C}$ and normal CXR or dyspnoea without another documented cause	
2	At least 2 of: productive cough/ bronchospasm/ $\text{SpO}_2 < 90\%$ on room air/ hypercarbia requiring treatment ( $\text{PaCO}_2 > 50$ mm Hg)/ atelectasis with gross radiological confirmation and a temperature of $> 37.5^{\circ}\text{C}$ and abnormal lung findings	
3	At least 1 of: pleural effusion requiring thoracentesis / pneumonia / pneumothorax / extended period of NIV / re-intubation lasting $< 48$ hours	Major
4	Mechanical ventilation $> 48$ hours prolonged after ICU arrival or due to re-intubation	
5	Death	

**Table 9. Post-operative pulmonary complication score**

The post-op pulmonary complication score was dichotomized into minor ( $\leq 2$ ) and major ( $\geq 3$ ) complications in order to calculate the sample size required. To identify a reduction in the incidence of major pulmonary complications by 15%, 320 patients were required to achieve 90% power at a 5% significance level.

Of the 4,483 patients assessed for eligibility, 53% ( $n = 2,391$ ) were excluded because they either had a previous history of cardiac surgery or they did not meet the  $\text{PaO}_2:\text{FiO}_2$  ratio criteria. 7% ( $n = 320$ ) of the total number of patients assessed were eventually recruited. Patients were randomised in a 1:1 ratio to either an intensive ( $n = 157$ ) or a moderate alveolar recruitment strategy ( $n = 163$ ).

Lung protective ventilation, based on a  $V_t$  of 6 ml/kg predicted ideal bodyweight (IBW), was employed in both groups as standard; however, the intensive group were maintained with a PEEP of 13 cm  $\text{H}_2\text{O}$  vs. 8 cm  $\text{H}_2\text{O}$  in the moderate group. Ventilation in the intensive group was maintained with either assist-controlled or pressure-controlled ventilation whilst the moderate group were maintained with either assist-controlled or

volume-controlled ventilation. Pressure-volume (PV) loops were performed to assess lung compliance at baseline and at 4 hours post-randomisation. Each group had a recruitment manoeuvre performed immediately after the acquisition of the PV loop i.e. a total of 2 recruitment maneuvers were performed in each group (Table 10). Mechanical ventilation was weaned after the second recruitment manoeuvre in both groups by progressive reduction of pressure support whilst maintaining the PEEP to that which the patient was randomised.

Recruitment Manoeuvre	Intensive Recruitment Strategy	Moderate Recruitment Strategy
No. of Inflation Cycles	3	3
Duration of Cycles (s)	60	30
Time Between Cycles (s)	60	60
PEEP (cm H <sub>2</sub> O)	30	20
Ventilation Mode	Pressure Control	CPAP
Ti (s)	1.5	-
Driving Pressure (cm H <sub>2</sub> O)	15	-
Resp Rate (breaths/min)	15	-
FiO <sub>2</sub>	0.4	0.6

**Table 10. Ventilatory settings**

60% (n = 195) of study participants were male with a mean age of 62.5 years. Groups were well matched at baseline in terms of co-morbidities, left ventricular function and renal function. Approximately 25% of patients in each group were smokers. 73% (n = 235) of patients underwent CABG with the remainder undergoing either valvular surgery (n = 71) or a combination of both (n = 14). The median pre-operative EuroSCORE was 3 (2-5) in each group indicating most patients were of medium risk with an estimated operative mortality of around 5%. 84% (n = 269) had surgery involving cardiopulmonary bypass.

The median pulmonary complication score was 1.7 (1.0-2.0) vs. 2.0 (1.5-3.0) in the intensive vs. moderate treatment groups respectively, (OR 1.86; 95% CI, 1.22 to 2.83. P = 0.003). Although secondary outcome measures only, there were non-statistically significant differences in favour of patients in the moderate treatment group staying longer in the ICU (4.8 days vs. 3.8 days) and hospital (12.4 days vs. 10.9 days) than those in the intensive group. The intensively treated group had a greater transient drop in blood pressure during the recruitment manoeuvre but by 5 minutes post-procedure this had resolved.

Post-hoc analysis revealed more patients in the moderate treatment group developed a pulmonary complication score of  $\geq 3$ , 26.4% (n = 43) vs. 15.3% (n = 24), (absolute difference, -11.1; 95% CI, -19.8 to -2.2). Further post-hoc exploratory analyses revealed daily post-operative pulmonary complication scores were lower in the intensive group on each of the first five post-operative days. Patients in the intensive group had a lower incidence of post-operative hypoxia on room air requiring supplemental oxygen, 59% (n = 93) vs. 77% (n = 125); OR, -17.5; 95% CI, -27.2 to -7.2. P = 0.001). The intensive group of patients also had a reduction in the need for extended non-invasive ventilation 4% (n = 6) vs. 15% (n = 25); OR, -11.5; -95% CI, 17.2 to -5.2. P < 0.001) in the post-operative period.

## Critique

This study is a welcome addition to the growing literature base on alveolar recruitment in the perioperative period. By recruiting postoperative cardiac surgical patients, most of whom had been subjected to cardiopulmonary bypass intraoperatively, the investigators ensured a homogenous group of patients with a low pulmonary compliance at baseline were recruited. Given the strict entry criteria and single centred nature of the trial, results cannot and should not be generalized to other patient groups.

Baseline lung compliance was 42.3 ml/cm H<sub>2</sub>O vs. 41.6 ml/cm H<sub>2</sub>O in the moderate vs. intensive groups, respectively. Once admitted to the ICU, both groups were ventilated with lung protective ventilation (6 ml/kg IBW). Lung compliance improved throughout the study period in both study groups but particularly so in the intensive group as evidenced by the pressure-volume loops. The supplementary material provides ventilation maps which were constructed via electrical impedance tomography carried out on the last 33 successively recruited patients to the trial. These detail beautifully how ventilation and compliance in dependent areas of lung improved steadily over time, particularly in the intensively treated group.

The intra-operative ventilatory management of this study deserves analysis. Maintenance ventilation was with a Vt of 8 ml/kg IBW and PEEP of 5 to 8 cm H<sub>2</sub>O. Only 29% (n = 93) of patients in this trial had an intraoperative recruitment manoeuvre performed which seems very low considering 85% were subjected to cardiopulmonary bypass and all had open chest surgery. Would baseline lung compliance have been as low if more patients had received an intraoperative recruitment manoeuvre? Did the lack of intraoperative lung recruitment maneuvers automatically disadvantage this patient group predisposing them to a low PaO<sub>2</sub>:FiO<sub>2</sub> on admission to ICU?

The definition and criteria of PPCs can vary widely between studies. This study used an ordinal scale as a severity scoring system which had been used in previous studies but



was originally developed in a cohort of patients suffering from severe COPD (a subgroup of patients who were actually excluded from this trial). A strict definition of pneumonia was employed and scheduled CXRs were reviewed independently by two respiratory experts who were blinded to treatment allocation. We are not told, however, of the level of agreement between these blinded assessors. Post-operative pulmonary function tests performed by spirometry may have arguably been a more objective primary outcome measure and may have given a clearer idea of how higher PEEP and recruitment manoeuvres affected lung function in either group.

Only a small proportion of patients in either group required re-intubation or mechanical ventilation for more than 48 hours (score  $\geq 4$ ). When minor postoperative pulmonary complications are considered (a score  $\leq 2$ ), the moderate group had 74% (n=120) of patients affected compared with 85% (n = 133) of the intensively treated group. Duration of postoperative mechanical ventilation in both groups was short - a mean of just 10.6 hours (9.6 -11.3) vs. 11.7 hours (10.8 - 12.5) in the intensive vs. moderate groups respectively. Among those with a postoperative pulmonary complication score of  $\geq 4$ , the reasons for re-intubation or prolonged mechanical ventilation are not given so it is unclear whether prolongation of mechanical ventilation or re-intubation was due to hypoxia, delirium, bleeding or some other cause. Postoperative pain scores, delirium scores, vasopressor requirement and fluid balance for each group are not given but would allow for a greater understanding of why some patients remained intubated or required re-intubation in each group.

### **Where this sits in the body of evidence**

The IMPROVE trial was a multicentre, double blind, randomised controlled trial carried out in seven French hospitals.<sup>5</sup> This study involved 400 patients undergoing elective abdominal surgery, the indication for which, in the majority of cases, was for an intra-abdominal cancer. The treatment group (n = 200) received Vt of 6 to 8 ml/kg IBW, PEEP 6 to 8 cm H<sub>2</sub>O and a recruitment manoeuvre of 30 cm H<sub>2</sub>O lasting 30 seconds every 30 minutes post-intubation. The control group (n = 200) were ventilated with Vt of 10 to 12ml/kg IBW and 0 PEEP. No post-intubation recruitment maneuvers were performed in the control group. The primary outcome was a composite of pulmonary and extra-pulmonary complications occurring within the first 7 days after surgery. The primary outcome occurred in 10.5% (n = 21) vs. 27.5% (n = 55) in the treatment vs. control groups, respectively (RR 0.4; 95% CI, 0.24 to 0.68; P = 0.001). Length of stay was shorter and fewer patients in the lung protective ventilation group required NIV or reintubation for active respiratory failure.

The PROVHILO study involved 30 centres across 10 countries in Europe, North and South America. This randomised, double blind, parallel group study involved patients

undergoing a laparotomy.<sup>6</sup> The ARISCAT score was used to include only patients who were deemed to be of intermediate or high risk of developing a postoperative pulmonary complication. Two thirds of the operative procedures were for cancer surgery. 900 patients were randomised to ventilation with a high PEEP (12 cm H<sub>2</sub>O) or a low PEEP ( $\leq$  2 cm H<sub>2</sub>O). Both groups were ventilated with a Vt of 8ml/kg IBW. The high PEEP group could also undergo intraoperative recruitment maneuvers which was prohibited in the low PEEP group. The primary endpoint was a composite of postoperative pulmonary complications by postoperative day 5. The primary endpoint occurred in 40% (n = 174) in the high PEEP group compared to 39% (n = 172) in the low PEEP group (RR 1.01; 95% CI, 0.86 to 11.2; P = 0.86). Those in the high PEEP group had more episodes of intraoperative hypotension and a greater need for vasopressors than those in the low PEEP group.

Severgnini et al in a small, single centred, open-label, randomised controlled trial recruited 56 patients undergoing elective, open abdominal surgery lasting for > 2 hours.<sup>8</sup> Patients were randomised to intraoperative ventilation of 9 ml/kg IBW with 0 PEEP (control group, n = 28), or to 7 ml/kg IBW and PEEP of 10 cm H<sub>2</sub>O (intervention group, n = 28). The intervention group were also allowed to have recruitment maneuvers performed intraoperatively. The intervention group had lower modified clinical pulmonary infection scores on days 1 and 3 compared to the control group.

A Cochrane Review of intraoperative use of low tidal volume ventilation in patients without evidence of acute lung injury included 12 studies and 1,012 patients.<sup>9</sup> The overall quality of the included trials was moderate. The included studies were all randomised controlled trials but the majority were single centred involving a small number of patients. Low Vt was defined as  $\leq$ 10 ml/kg IBW. The investigators concluded that low Vt ventilation reduces the risk of both invasive and non-invasive ventilation being required in the postoperative period but had no effect on length of hospital stay or 30 day mortality.

The ART trial, a non-blinded RCT involving 120 ICUs in 9 different countries, compared the effect of a lung recruitment manoeuvre and titrated PEEP according to best respiratory system compliance, to a lung protective ventilatory strategy with a lower PEEP in 1,013 patients suffering from ARDS.<sup>10</sup> All-cause 28 day mortality was 55.3% (n = 277) vs. 49.3% (n = 251) in the experimental vs. control groups respectively (HR, 1.2; 95% CI, 1.01 to 1.42; P = 0.041). This trial does not support the use of aggressive recruitment manoeuvres and PEEP titration in patients with moderate/severe ARDS. (*This trial is described in detail in the preceding chapter*)

The PHARLAP trial (**P**ermissive **H**ypercapnia, **A**veolar **R**ecruitment, **L**ow **A**irway **P**ressures, NCT01667146) is a multi-centre RCT comparing an open lung strategy using a daily staircase recruitment manoeuvre and individualised PEEP titration with lung protective ventilation as per the ARDSNET protocol. The primary outcome measure is the number of ventilatory free days at day 28 post randomisation. Due to the results of the ART trial, PHARLAP ceased recruiting in mid October 2017 on safety grounds. Results are due sometime in 2018.

**Should we routinely use recruitment manoeuvres as described in this trial to prevent post operative pulmonary complications.**

Possibly. In contrast to the open lung strategy employed by the ART trial, a more conservative approach was successfully used in this trial. Further data is required to clarify the role of recruitment manoeuvres in ventilatory management.

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## APRV

**Zhou Y, Jin X, Lv Y, Wang P, Yang Y, Liang G et al. Early application of airway pressure release ventilation may reduce the duration of mechanical ventilation in acute respiratory distress syndrome. *Intensive Care Med* 2017;43(11):1648-1659**

### Introduction

Seventeen years after the landmark ARDSnet paper established that mechanical ventilation at a 6ml/kg set tidal volume was superior to 12 ml/kg in patients meeting criteria for the acute respiratory distress syndrome (ARDS)<sup>1</sup> uncertainty and controversy remain. Whether the optimal tidal volume for controlled ventilation may be lower still remains an area of active research,<sup>2</sup> but population studies consistently show that many patients with ARDS receive ventilation at significantly higher tidal volumes.<sup>3</sup> An overriding issue may be that ARDS is defined by descriptive clinical and radiological criteria rather than specific evidence of alveolar injury, increasing heterogeneity in study populations.

Two specific areas of current uncertainty are the timing of the transition to spontaneous ventilation and the optimal set level of positive end-expiratory pressure (PEEP) (individually or at a population level).<sup>4</sup> Spontaneous ventilation modes may improve patient-ventilator synchrony with less sedation need, but risk uncontrolled tidal volumes and high respiratory rates causing over-distension and atelectrauma.<sup>5</sup> PEEP raises mean inspiratory airway pressure and prevents bronchio-alveolar collapse, improving oxygenation at the expense of potential compromise of venous return and right ventricular function.<sup>6</sup> Airway pressure release ventilation (APRV) can be conceptualised as an extreme inverse-ratio time-cycled bilevel pressure ventilation; with a high mean airway-pressure aiming to aid oxygenation and alveolar recruitment in a similar manner to PEEP; with carbon dioxide (CO<sub>2</sub>) clearance assisted by unrestricted spontaneous ventilation alongside brief intermittent pressure releases. Its use in patients with ARDS has been led by enthusiasm rather than rigorous evidence of benefit.<sup>7</sup>

### Synopsis

This was a single-centre, randomised controlled trial comparing APRV against low tidal-volume lung protective ventilation (LTV) in patients with ARDS conducted in the West China Hospital of Sichuan University, China. Eligible patients were receiving mechanical ventilation for  $\leq 48$  hours, had a PaO<sub>2</sub>:FiO<sub>2</sub> ratio of  $\leq 250$  mm Hg and met the Berlin diagnostic criteria for ARDS.<sup>8</sup> Patients with pregnancy, neuromuscular disorders, extremes of age ( $< 18$  or  $> 85$  years old), receiving extracorporeal support, a suspected duration of mechanical ventilation  $< 48$  hours or suspected non-survival in ICU (or within

6 months) were excluded. Also excluded were those with relative contra-indications to APRV: barotrauma or severe chronic obstructive pulmonary disease (COPD) (due to the restriction of expiration) and intracranial hypertension (due to the lack of CO<sub>2</sub> control). Randomisation was by selection of an envelope containing a computer-generated random allocation.

The ventilators (Puritan Bennet™ 840, Covidien, Medtronic Inc., Minneapolis, US) were managed by respiratory therapists. Initially all patients received volume assisted-controlled ventilation (VCV) aiming to achieve a PaO<sub>2</sub> 55-100mmHg (or SpO<sub>2</sub> 88%- 98%), arterial pH ≥7.30 and a plateau airway pressure (P<sub>plat</sub>) ≤ 30 cm H<sub>2</sub>O; these targets remained goals throughout the study. Those randomised to LTV received VCV in line with the ARDSnet protocols; with a target tidal volume (V<sub>T</sub>) of 6 ml/kg predicted body weight (PBW), PEEP chosen from a PEEP-FiO<sub>2</sub> table and respiratory rate titrated to the target pH. If P<sub>plat</sub> allowed V<sub>T</sub> was also allowed to be adjusted between 4-8 ml/kg IBW to aid pH control. If oxygenation deteriorated PEEP was adjusted at clinician discretion, if severe respiratory acidosis (pH <7.15) ensued despite a respiratory rate of 35 /min tidal volumes could be increased beyond a P<sub>plat</sub> of 30 cm H<sub>2</sub>O and/or sodium bicarbonate could be given. Those randomised to APRV received the initial settings detailed in table 11.

APRV Parameter	Initial Setting
High airway pressure (P <sub>high</sub> )	Set at P <sub>plat</sub> measured during VCV (≤ 30 cm H <sub>2</sub> O)
Low airway pressure (P <sub>low</sub> )	5 cm H <sub>2</sub> O
Duration of release phase (T <sub>low</sub> )	1 – 1.5 X expiratory time constant, adjusted by PEFR measurement to ≥ 50% PEFR
Release frequency	10 – 14 /minute
Duration of P <sub>high</sub> (T <sub>high</sub> )	Dependent (on T <sub>low</sub> and release frequency)
Target spontaneous minute ventilation (MV <sub>spont</sub> )	30% of total minute ventilation (MV <sub>total</sub> )

**Table 11. Initial APRV settings**

Patients in both groups were sedated to a Richmond Agitation-Sedation Scale (RASS) score of -2 to 0, deepened if they exhibited anxiety, agitation or respiratory distress. Recruitment maneuvers, prone positioning, neuromuscular blockade or inhaled nitric oxide were allowed as rescue therapies for severe hypoxaemia (PaO<sub>2</sub>:FiO<sub>2</sub> ≤ 100 mmHg), with extracorporeal support or high frequency oscillatory ventilation (HFOV) reserved for those with: PaO<sub>2</sub> ≤ 55 mmHg with FiO<sub>2</sub> 1.0; refractory shock; acidosis; and unresolving pneumothorax or air leak after pleural drainage. Patients in the LTV group underwent a sedation hold and a spontaneous breathing trial (SBT) safety screen each morning, those passing underwent a SBT with pressure support ventilation for 30 minutes. Those in the APRV group had P<sub>high</sub> and release rate progressively reduced by 2 cm H<sub>2</sub>O and 2/min,

respectively twice daily as tolerated; and transitioned to the same SBT when a  $\text{FiO}_2$  of 0.4 and  $\text{P}_{\text{high}}$  20 cmH<sub>2</sub>O were achieved. Those successfully passing the SBT were assessed for extubation by the physician and respiratory therapist.

The chosen primary outcome was the number of ventilator-free days (VFDs) at day 28 (set at zero if the patient died before then). Preset secondary endpoints included clinical outcomes (including mortality) and respiratory mechanics. The power calculation was based on the VFDs found in an ARDSnet trial of PEEP strategies and a small study suggesting APRV shortened the duration of mechanical ventilation in trauma patients by 6 days. Enrolment of 110 patients was calculated to have 80% power (2-sided  $\alpha = 0.05$ ) to detect a 5-day increase in VFDs with APRV.

138 of 251 screened patients were enrolled over 16 months from May 2015. Raised intracranial pressure and an expectation of early extubation were the commonest exclusion reasons. In the APRV group ( $n = 71$ ) 70% were male, mean age was 52 years, 32% had a significant co-morbidity and mean ( $\pm$  SD) APACHE II score was  $22 \pm 8$ . Baseline mean  $\text{PaO}_2:\text{FiO}_2$  was  $122 \pm 47$  mm Hg, and  $< 150$  mm Hg in 66%. ARDS was caused by pneumonia in 25%, sepsis in 18%, pancreatitis in 27% and trauma or surgery in 24%. Mean baseline ventilation parameters were: set tidal volume  $7.2 \pm 0.7$  ml/kg predicted body weight;  $\text{FiO}_2$   $0.66 \pm 0.19$ ; PEEP  $11.4 \pm 33.0$  cm H<sub>2</sub>O; plateau pressure  $26.5 \pm 4.0$  cm H<sub>2</sub>O, respiratory rate  $21.5 \pm 7$  /min. Characteristics in the LTV group ( $n = 67$ ) were similar, excepting a higher rate of co-morbidity (51% vs. 32%;  $P = 0.03$ ), a 39% incidence of pneumonia as the cause of ARDS, a higher baseline mean  $\text{PaO}_2:\text{FiO}_2$  of  $138 \pm 56$  and a slightly lower respiratory rate of  $19.5 \pm 5$  /min. All patients were included in the intention-to-treat analysis, 20 were excluded from the per-protocol analysis (14 transferred to another hospital, 3 with care withdrawn  $<24$  hours after enrolment and 3 patients crossed over (2 from LTV ventilation to APRV)).

Patients in the APRV group had significantly more VFDs by day 28 than those in the LTV group (primary outcome; median (IQR) 19 (8-22) days vs. 2 (0-15) days;  $P < 0.001$ ), with a similar difference seen on per-protocol analysis. More patients receiving APRV were successfully extubated (66% vs. 39%;  $P=0.001$ ) and fewer required tracheostomy (13% vs. 30%,  $P = 0.013$ ). There was no difference in the incidence of pneumothorax; 3 vs. 7 in the APRV vs LTV groups, respectively ( $P = 0.199$ ). Neuromuscular blockade, prone positioning, nitric oxide or HFOV was required in 23 (34%) patients in the LTV arm and 6 (8%) receiving APRV. Length of stay was significantly reduced in ICU (APRV vs. LTV 15 vs. 20 days,  $P = 0.015$ ) but not hospital (21 vs. 27 days,  $P = 0.06$ ). ICU mortality (20% vs. 34%;  $P = 0.06$ ) and hospital mortality (24% vs. 37%;  $P = 0.09$ ) were not significantly reduced with APRV.

Respiratory variables also differed between the groups. At day 3 patients receiving APRV had a significantly lower  $\text{FiO}_2$  ( $0.43 \pm 0.09$  vs.  $0.53 \pm 0.19$ ;  $P = 0.001$ ) and higher mean airway pressures ( $22 \pm 3.5$  vs.  $16 \pm 3.3$  cm H<sub>2</sub>O;  $P < 0.001$ ) and  $\text{PaO}_2:\text{FiO}_2$  ratios ( $280 \pm 84$  vs.  $180 \pm 69$  mmHg,  $P < 0.001$ ). When temporarily switched back to VCV the APRV group had significantly lower plateau pressures ( $19 \pm 4$  vs.  $23 \pm 5$  cmH<sub>2</sub>O;  $P < 0.001$ ) and higher respiratory compliance ( $44 \pm 11$  vs.  $34 \pm 9$  ml/cm H<sub>2</sub>O;  $P < 0.001$ ). There was no difference in pH or  $\text{PaCO}_2$  ( $41 \pm 7$  vs.  $42 \pm 9$  mm Hg;  $P = 0.291$ ) between groups. These differences persisted to day 7. Patients receiving APRV also had a lower mean heart rate ( $93 \pm 17$  vs.  $104 \pm 19$  /min;  $P = 0.001$ ) and higher mean arterial pressure (MAP) ( $93 \pm 15$  vs.  $87 \pm 14$  mmHg;  $P = 0.032$ ), noradrenaline doses were similar. Finally at day 3 and day 7 APRV patients were significantly less sedated by RASS scoring and receiving less sedatives by infusion (statistically significant for midazolam and fentanyl but not propofol).

## Critique

There are a number of obvious points which should cause the between-group differences of this investigation to be interpreted with caution. This was a single-centre study with relatively small numbers with a primary endpoint of ventilator-free days which is a surrogate for more important patient-centred outcomes. The small number of patients recruited means that rare, but serious adverse effects of either therapy, may have been missed. In addition, the small sample size led to an imbalance in the rate of co-morbidity in favour of the APRV group, which may have been a confounding factor. The trial was conducted in China, which may imply differences in both the patient population and the nuances of the health-care system or general ICU care to that found in the West. Those treating the patients were unblinded to the treatment allocation, which was probably unavoidable in this case but raises the possibility of conscious or unconscious bias affecting key outcomes such as the medical decision of the timing of extubation.

There are also aspects of the methodology which require examination. Tidal volumes of up to 8 ml/kg were allowed in the LTV group which is 33% higher than that successfully used in the original ARDSnet study (although it may more accurately reflect usual practice).<sup>3</sup> Sedation targets were identical in both groups, despite the suppression of spontaneous ventilation being a frequent intentional aim with LTV ventilation for severe ARDS and normally undesirable with APRV. It is uncertain why the initial  $P_{\text{low}}$  was set at 5 cmH<sub>2</sub>O; a  $P_{\text{low}}$  of zero is commonly advocated with APRV in order to minimise resistance to expiratory flow during passive lung recoil.<sup>9,10</sup> ICU ventilators differ in the way that APRV settings can be modified – it may not be easy on all models to adjust  $T_{\text{low}}$  based on the Peak Expiratory Flow Rate (PEFR). The evidence-base for prone ventilation and neuromuscular blockade as rescue therapies for severe hypoxia is as an add-on therapy to LTV; and patients receiving APRV requiring these should perhaps have been switched



to traditional ventilation. Follow-up of those transferred to local hospitals (14 patients) was by telephone and may have been less accurate. Finally, any study in which time-to-extubation is an important outcome is vulnerable to any superiority of the weaning protocol used in each group.

Nevertheless this is an intriguing study with many strengths and a welcome addition to the literature. The patient population met the modern criteria for ARDS.<sup>8</sup> LTV was delivered in a manner approaching current best practice.<sup>4</sup> The study population is well described and randomisation seemed appropriate. Follow-up was complete and only 3 patients (2%) crossed-over between ventilation modes. Although a per-protocol analysis was performed, the intention-to-treat population was used for the main endpoints. The primary outcome of ventilator-free days and other clinical endpoints were significantly affected in favour of APRV. Patients receiving APRV were more likely to be extubated successfully and at an earlier stage, with less need for a tracheostomy or intervention for severe hypoxia. Whilst the study was not powered to examine mortality there was no signal suggesting any increase in this or other adverse outcomes.

APRV has been in clinical use for over 30 years but there is a remarkable paucity of randomised controlled trials evaluating its utility in critically ill humans.<sup>7</sup> Reported benefits of the therapy include better oxygenation due to alveolar recruitment (high mean airway pressures); improved ventilation / perfusion matching (preserved diaphragmatic function with spontaneous ventilation); reduced lung stress (lower respiratory rate avoiding atelectrauma); increased patient comfort and reduced work of breathing.<sup>7,10</sup> The increased elastic recoil of non-compliant lung seen in ARDS has been suggested to improve the CO<sub>2</sub> clearance of the release breaths.<sup>9</sup> Data supporting these benefits is largely based on animal studies and case series.

APRV use in clinical practice has been driven by clinician enthusiasm rather than consensus guidelines; with some centres utilising it as their default mode of ventilation and others using it more sparingly. There are many critical care therapies which have been similarly introduced but not stood the test of time.<sup>11</sup> The results achieved by Zhou and colleagues are in contrast to previous randomised studies which have suggested an increased time to extubation with APRV, and it must be remembered there is a wealth of data showing improved outcomes with LTV in ARDS.<sup>4</sup> With this in mind (alongside the baseline inequalities in favour of APRV) repetition of this study in a large / multi-centre setting would be advisable.

## **Where this sits in the body of evidence**

Much of the data supporting the physiological claims made for APRV arises from studies in animals.<sup>7</sup> Previous data in humans is limited to case series and small randomised controlled trials (RCTs), many from trauma ICUs in the US.

## **Where this sits in the body of evidence**

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Räsänen in 1991 reported on a prospective multi-centre non-randomised study wherein 50 adults with respiratory failure received short-term APRV and conventional ventilation sequentially<sup>12</sup>. APRV was adjusted to deliver a similar mean airway pressure to that during conventional ventilation, and achieved similar oxygenation targets with a significant reduction in peak airway pressure. Patient outcomes were not reported.

In 2008 Fan published a prospective observational study examining sedation use in 165 mechanically ventilated patients from 9 ICUs in 3 Baltimore (US) hospitals.<sup>13</sup> The 17 patients managed with APRV received significantly less sedative medications (predominantly midazolam and fentanyl) than the 148 patients managed with assist-control ventilation (ACV). Those receiving APRV had a significantly longer ICU length of stay (14 vs. 10 days;  $P=0.04$ ) and lower ICU mortality (12% vs. 48%;  $P=0.004$ ). APRV was used in 16/17 surgical ICU patients and 3/148 from medical ICUs, limiting interpretation.

Maung et al from Connecticut (US) in 2012 reported a retrospective review of 309 trauma patients successfully weaned from mechanical ventilation utilising APRV ( $n=75$ ) or ACV ( $n=234$ ).<sup>14</sup> APRV was associated with a longer time to extubation (19.6 vs. 10.7 days;  $P<0.001$ ) which remained significant on multiple linear regression analysis. The hospitals had weaning protocols in place for ACV but not APRV.

Maxwell from Tennessee (US) in 2010 published the first exploratory prospective RCT comparing APRV and LTV use in ventilated ICU patients.<sup>15</sup> 66 patients were enrolled, 3 were excluded from the analysis for protocol violations; 17 met the criteria for ARDS. There were no differences found between those assigned to APRV or LTV for clinical outcomes (ventilator days, ICU length of stay, mortality, sedation use, incidence of tracheostomy or pneumothorax). However, at 72 hours after randomisation 30/32 patients assigned to LTV had transitioned to CPAP/pressure-support ventilation (PSV).

In 2009 Yoshida published a small retrospective study using computerised tomography (CT) scans to compare lung aeration in patients receiving APRV or PSV.<sup>16</sup> 18 patients with

ARDS were identified who had received 2 helical CT scans within 3 days and remained on APRV or PSV for that period. On their second CT those receiving APRV had less atelectasis (19% vs. 41%,  $P=0.008$ ) and more normally aerated lung units (43% vs. 29%;  $P=0.008$ ). These changes were not seen in those receiving PSV and oxygenation outcomes did not differ between groups.

Putensen and colleagues in 2000 reported on 30 German patients with trauma who were randomly assigned to APRV or pressure-control ventilation (PCV) with suppression of spontaneous ventilation by increased sedation and neuromuscular blockade.<sup>17</sup> 5 (17%) had ARDS. Those receiving APRV had higher respiratory compliance and oxygenation; increased pulmonary artery catheter-measured cardiac index and oxygen delivery; and were discharged from ICU sooner.

Andrews et al from Baltimore (US) utilised APRV routinely in ventilated trauma patients and in 2013 compared retrospective data from their own institution to summary data derived from a systematic review of trauma patients from other institutions.<sup>18</sup> The dataset comprised 66,199 patients from 16 studies all reporting the incidence of ARDS and hospital mortality; but not with standardised (or even reported) ventilatory strategies. The authors APRV-managed patients had a lower incidence of both diagnosed ARDS (1.3% vs. 14%) and mortality (3.9% vs. 14.1%) than the population mean despite higher-than average injury severity scores.

### **Should we be using APRV as our default ventilatory mode in ARDS?**

No, and those utilising it should be aware that despite its potential benefits and the encouraging results of this study its safety is not firmly established. More studies are urgently required.

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# Gastrointestinal Trials



## REVISE

**Alhazzani W, Guyatt G, Alshahrani M, Deane A, Marshall J, Hall R et al. Withholding Pantoprazole for Stress Ulcer Prophylaxis in Critically Ill Patients: A Pilot Randomised Controlled Trial and Meta-analysis. Crit Care Med 2017;45(7):1121-1129**

### Introduction

Mechanical ventilation for more than 48 hours and coagulopathy are the two main predisposing factors for stress ulceration in the critically ill patient. Although gastric mucosal stress ulceration is felt to be common in ICU patients, most are clinically insignificant and account for only a small proportion of cases of upper gastrointestinal (GI) bleeding.<sup>1</sup> Stress ulcers arise via a number of mechanisms, including hypoperfusion, oxidative stress and overproduction of gastric acid.<sup>2</sup> Difficulties with the identification of gastric mucosal ulceration result from differing definitions of “significant bleeding” and variation in the confirmation of bleeding via oesophagogastroduodenoscopy (OGD) and/or angiography. The true incidence is unknown.

International guidelines now strongly recommend stress ulcer prophylaxis (SUP) for ICU patients with risk factors for stress ulceration.<sup>3</sup> Proton pump inhibitors (PPIs) or H<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs) are the principle agents used to achieve SUP, with recent surveys suggesting PPIs are more often prescribed.<sup>4</sup>

The evidence base for the ubiquitous use of SUP has been recognised as being of low quality. Modern goals of intensive care therapy include early enteral feeding and lung protective ventilation. Early enteral nutrition is thought to have a protective effect on the gastric mucosa, although this has not been confirmed.<sup>4</sup> PPI prophylaxis may not be a benign intervention. The increase in gastric pH associated with PPI use may result in migration of microbes into the GI tract and disruption of normal gut flora. Ventilator-associated pneumonia (VAP) and *Clostridium difficile* infection have a higher incidence among patients who have been prescribed PPIs.<sup>5</sup>

To try and further evaluate the effectiveness and the incidence of adverse effects associated with the use of PPIs, a number of large, multicentre, randomised controlled trials are underway (NCT02467621, NCT02929563, 1415-01 - ANZICS CTG study number).<sup>1</sup> The results of these trials will help clarify who benefits from SUP prescription, but perhaps more importantly, which patients do not benefit, or indeed come to harm.

### Synopsis

REVISE, a multi-centre, randomised, double-blind, placebo controlled trial, was designed

to assess the feasibility of conducting larger trials which will assess the impact of stress ulcer prophylaxis (SUP) on important clinical outcomes. Ten tertiary referral, university-affiliated ICUs contributed to patient recruitment and data collection.

Adult patients admitted to ICU who were expected to remain intubated for more than 48 hours were eligible for inclusion. Patients prescribed proton pump inhibitors due to active bleeding were excluded, as were those on dual antiplatelet agents. Patients were randomised in a 1:1 ratio, to either pantoprazole 40 mg IV once daily (control group) or to placebo (intervention group). Stratification for centre, whether PPI or H<sub>2</sub>RA naive or not and, for those taking SUP, whether a PPI or H<sub>2</sub>RA was continued or discontinued.

As a pilot study, the primary outcomes were feasibility related. A recruitment rate of at least 2 patients per centre per month, a consent rate of at least 70% and a protocol adherence rate of at least 80% were targeted. Secondary outcomes included incidence of clinically important GI bleeding (Table 12), incidence of ventilator-associated pneumonia (VAP) and rate of *C. difficile* infection. ICU and hospital length of stay, and mortality rates were also secondary outcome measures.

Overt GI Bleed	Accompanying Features (within 24 hours)
Haematemesis	Drop in SBP or DBP of $\geq 20$ mm Hg
Coffee grounds aspirate from nasogastric tube	Orthostatic increase in pulse $\geq 20$ beats/min and a decrease in SBP of $\geq 10$ mm Hg
Melaena	Decrease in Hb of $\geq 2$ g/dL
Haematochezia	Transfusion of $\geq 2$ units of packed cells

**Table 12. Clinically significant GI bleed**

*Clinically significant GI bleed = overt GI bleed +  $\geq 1$  accompanying feature. SBP & DBP = systolic / diastolic blood pressure; Hb = haemoglobin*

Of 150 patients assessed, 91 were randomised. Physician or surrogate decision makers declining the invitation to enter the trial accounted for the majority of exclusions (n = 39). All 49 patients randomised to the pantoprazole group received the drug. Forty-two patients were randomised to the placebo group, of whom 40 received the intervention. The drug was continued intravenously whilst the patient was mechanically ventilated, but was stopped if a GI bleed occurred. There were no patients lost to follow-up.

77% (n = 70) of patients were medical with 37% (n = 34) prescribed a PPI or H<sub>2</sub>RAs prior to recruitment. Patients were well matched between groups for age, sex and APACHE II score (median 21). Prescription of anticoagulant drugs and NSAIDS was similar between



groups. 50.5% (n = 46) were receiving vasopressors at baseline and all were mechanically ventilated. 89% (n = 81) of patients received enteral nutrition within 72 hours of inclusion.

All feasibility targets were met; 2.9 patients per centre per month were recruited with a mean consent rate of 77.8% and protocol adherence was 97.7% of study days. Although secondary outcome measures, there was no statistical difference in the rate of clinically important GI bleeding, 6.1% vs. 4.8%, in the pantoprazole and placebo groups, respectively (P ≈ 1.0). Similarly, there was no statistical difference in the rate of *C. difficile* infection (4.1% vs. 2.4%; P ≈ 1.0) or VAP (20.4% vs. 14.3%; P = 0.58). ICU mortality was similar between groups, (22.4% vs. 23.8%; P = 0.6), in the pantoprazole and placebo groups, respectively. The median duration of study drug exposure was 5 days in both groups.

To gain an understanding of the current quality of evidence available on the topic of SUP in ICU, a literature search of randomised controlled trials (RCTs) comparing PPI to placebo, reporting at least one of the clinical outcomes of interest in REVISE, was also conducted. Five RCTs (excluding REVISE), totalling 602 patients were included. No difference in risk of GI bleeding, VAP, *C. difficile* or mortality was detected. Although bias was not an issue with any of the trials included in the meta-analysis, the quality of evidence was rated as low due to serious imprecision in each trial.

## Critique

This was a well conducted, multicentre, randomised, controlled feasibility study, the results of which will inform the design of larger phase 3 RCTs. The pragmatic design of the study, with a high proportion of patients receiving early enteral nutrition and a high proportion of patients receiving either PPI or H<sub>2</sub>RA prior to admission reflects real world experience. Although most of the participating centres were based in Canada, a Saudi Arabian and an Australian centre also contributed. This trial has therefore demonstrated that SUP can be investigated in an international manner.

The randomisation process was robust with stratification for those who were prescribed PPI prior to admission, adding strength to the trial design. The blinding of staff involved with patient care, data collection and interpretation was also impressive. Clear definitions of clinically important GI bleeding, VAP and *C. difficile* infection were used.

This was a sick patient group, reflected in the APACHE score (median 21), rate of vasopressor use (50.5%), ICU mortality rate (23%) and duration of mechanical ventilation. However, the majority (77%, n = 70) of patients were admitted medically, and may not have been at very high risk of a GI bleed. One of the challenges of future

multicentre trials will be to assess the role of PPIs on similar clinical outcome measures, in patients whose risk can be stratified as high, intermediate or low based on clinical, laboratory and other investigations. Surgical and trauma patients may not be as quickly established on enteral feeding and the risk of GI bleed may be higher in these patient groups. Instead of the present day ubiquitous use of PPIs, future trials should help clarify the role of PPIs in specific subsets of patients. Furthermore, future trials should help clarify the risk / benefit profile of PPIs in patients who may have other risk factors for *C. difficile* and/or VAP.

Patients in both groups received a median of 5 doses of study drug. The exposure dose of PPI required to increase the risk of VAP or *C. difficile* is unknown. The median duration of mechanical ventilation was 9 days (IQR 8 - 23) in the pantoprazole group and 6.5 days (IQR 3 - 15) in the control group. Although 89% (n = 81) of patients received early enteral feeding, the proportion of patients who were able to be established on the full rate of enteral feed, calculated according to their own specific energy requirements, is not known. Perhaps cessation of study drug in those patients reaching their individual target enteral nutrition rate would also better reflect real world experience. Knowledge of the proportion of patients receiving TPN, either as a sole source of nutrition, or in combination with enteral nutrition may also help in identifying those patients in whom establishing enteral nutrition has been challenging, and in whom the requirement for PPI cover may be greater.

Information regarding the 30° head-up position, sedation practices and weaning protocols is lacking in the main publication but may have an impact on the rate of VAP. Similarly, background information on the use of antibiotics, antibiotic surveillance programmes and rates of *C. difficile* among patients in participating units would be useful additional information to include for any phase 3 trial.

### **Where this sits in the body of evidence**

POP-UP was a single centre, randomised, double-blind, placebo-controlled, feasibility trial.<sup>6</sup> It was carried out in a mixed medical-surgical ICU. Patients were randomised to receive either a once daily dose of 40 mg IV pantoprazole or placebo. Only 13% (n = 216) of admitted patients were recruited as most were either not mechanically ventilated or extubated within 24 hours. The median number of study drug administrations was 3 in each group. Over 80% of patients received enteral nutrition within 16 hours of mechanical ventilation initiation. Almost all patients received study drug and 98% completed follow-up. As an exploratory study, POP-UP was underpowered to detect clinically important outcomes.

The association of PPI use and development of *C. difficile* infection was studied in a

single centre retrospective analysis of data from 3286 medical ICU patients in Germany.<sup>7</sup> 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 *C. 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 randomized controlled trials comparing H<sub>2</sub>RAs with placebo for SUP in ICU patients.<sup>8</sup> The primary endpoint was incidence of significant GI bleed and secondary endpoints were hospital-acquired pneumonia (HAP) and hospital mortality. 17 studies were included. Only 3 studies included patients with an adequate rate of enteral nutrition. SUP with H<sub>2</sub>RAs reduced the rate of clinically significant GI bleeding, (OR 0.47; 95% CI, 0.29 to 0.76; P < 0.002). The benefit in reduction of GI bleed was confined solely to those patients who were not enterally fed. If patients were enterally fed and received SUP, there was no reduction in GI bleeding but there was 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 performed an international multicentre inception cohort study over a 7 day period between December 2013 and April 2014.<sup>9</sup> 97 ICUs in 11 countries contributed to data collection from 1,034 patients. 73% of patients were prescribed a gastric acid suppressant with 573/1,034 (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 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 vs. H<sub>2</sub>RAs in SUP.<sup>10</sup> Primary outcome measures were clinically important and overt upper GI bleeding. Pneumonia and *C. 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. H<sub>2</sub>RA, (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. H<sub>2</sub>RA 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 H<sub>2</sub>RA or a PPI for 48

hours or more was analysed.<sup>5</sup> Primary outcomes were rates of GI bleeding, pneumonia and *C. difficile* infection, coded as secondary diagnoses as per the International Classification of Diseases, 9<sup>th</sup> Revision. 38.1% of patients in this databank received a H<sub>2</sub>RA 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 *C. difficile* (2.2% v 3.8%; P < 0.001) were lower in the H<sub>2</sub>RA group compared to PPIs.

Twenty randomised controlled trials involving 1,971 patients were included in another meta-analysis of SUP vs. placebo or no prophylaxis.<sup>11</sup> 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 included trials was low with a high risk of bias. No difference in mortality, GI bleeding or HAP was detected between SUP versus placebo or no prophylaxis.

A retrospective cohort study extracted data from a large Japanese database on SUP in patients admitted with severe sepsis.<sup>12</sup> Data was retrieved on over 70,000 patients from 526 hospitals. Propensity scores were used to create treatment (SUP) 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, *C. 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 these large phase III studies currently in progress, which will further enhance our understanding of this area.<sup>13</sup>

- SUP-ICU (NCT02467621) is a large European RCT which finished randomising 3,350 patients to PPI or placebo in October 2017. Results are expected in the first half of 2018. The primary outcome measure will be 90-day mortality.
- The ANZICS group is currently conducting a cluster-randomised, crossover trial, the PEPTIC trial (ANZICS CTG Number 1415-01). This trial will compare PPI with H<sub>2</sub>RA for SUP. The estimated sample size will be 40,000 with primary outcome measures of stress ulcer related bleeding, *C. difficile* infection and mechanical ventilation lasting more than 10 days.
- The Canadian PIC-UP trial is a feasibility study comparing PPI vs. placebo in the paediatric ICU population (NCT02929563). The estimated sample size is 120.

### **Should we implement this into our practice?**

No. We await the results of further large scale phase III studies to clarify the role of PPI prophylaxis for prevention of stress ulcers in mechanically ventilated ICU patients.

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# Nutrition Trials



## NUTRIREA-2

**Reignier J, Boisramé-Helms J, Brisard L, Lascarrou JB, Hssain AA, Anguel et al. N Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet 2017;epublished November 8th**

### Introduction

Nutritional support in the acutely ill patient is complex. Critical illness is typically associated with a catabolic stress resulting in increased energy demands, hyperglycaemia and muscle mass degradation.<sup>1</sup> Patients are at risk of malnutrition which is associated with poorer outcomes.<sup>2</sup> However, the optimal calorific intake, timing and route of delivery remain controversial.<sup>1</sup> Enteral nutrition is considered more physiological, with potential benefits on gut structure and immune function.<sup>3</sup> Furthermore, early initiation within 24 hours may improve patient outcomes.<sup>4</sup> Despite this, enteral nutrition has also been associated with gastrointestinal intolerance and underfeeding.<sup>5</sup>

Parenteral nutrition may be seen as a better route to secure nutritional requirements, but requires invasive intravenous access with potential complications. Administration of parenteral nutrients, particularly protein and lipid-enriched feeds, may also suppress autophagy leading to an increase in the accumulation of damaged mitochondria and toxic protein aggregates.<sup>6</sup> Previous meta analysis of enteral versus parenteral nutrition has concluded that enteral nutrition was associated with reduced infections, but not mortality.<sup>7</sup> Subsequently, guidelines have recommended enteral nutrition as the preferred route of nutritional support in intensive care patients.<sup>3,8</sup> Recent evidence has challenged these recommendations.

The CALORIES trial randomised 2,400 heterogeneous intensive care patients to either enteral or parenteral nutrition.<sup>9</sup> There was no difference in mortality or infective complications. By recruiting a more severely ill population than the CALORIES trial, the NUTRIREA-2 trial provides more important information on the effect of the route of nutrition supplementation in critical care patients.

### Synopsis

This was a multi-centre, randomised trial performed in 44 French intensive care units. The primary aim was to compare early enteral nutrition with parenteral nutrition in critically ill patients. Adults, expected to be ventilated for more than 48 hours, who required vasoactive support and could be commenced on nutritional support within 24 hours of intubation or intensive care admission, were eligible for recruitment. Patients



were excluded if they had gastrointestinal surgery within the previous month, active gastrointestinal bleeding, previous gastrointestinal surgery that could affect absorption or they required nutritional support at home. Patients were also excluded if they had a contraindication to parenteral nutrition, were pregnant or breastfeeding or had a treatment limitation.

Eligible patients were randomised within 24 hours using a secure web-based system to receive either early enteral or early parenteral nutrition in a 1:1 ratio, stratified by centre. Nutrition was prescribed to target a calorific intake of 20-25 kcal/kg/day for the first week, increasing to 25-30 kcal/kg/day thereafter using a standardised regime. In the parenteral group, nutrition was provided for the first 72 hours solely by the parenteral route; subsequently, if blood lactate was normal and vasopressors stopped for 24 hours, then enteral nutrition was commenced. On day 8, enteral nutrition was commenced regardless of haemodynamics, although this could be supplemented with parenteral feed. In the enteral group, nutrition was solely administered by the enteral route for the first week, with supplemental parenteral only allowed on day 8. Residual gastric volumes were not monitored. Training was provided on the study protocol and management of intolerance to enteral feeding.

The primary outcome was 28-day mortality. Secondary endpoints included the Sequential Organ Failure Assessment (SOFA) score; bodyweight; amounts of calories and proteins delivered; vomiting; prokinetic use; stool; blood glucose; insulin treatment; blood lactate; liver function tests; gastric ulcer prophylaxis; acquired infections and antibiotic use; prone position; dialysis during the intervention period; day 90, ICU and hospital mortality; ICU and hospital length of stay; days without life support and any noninfectious complications. Complications were diagnosed using predefined criteria.

Based on data from the NUTRIREA-1 study, assuming a 37% 28-day mortality rate in the parenteral group, a sample size of 2,854 patients was calculated to give 80% power with a 4.9% two-sided type 1 error rate to detect a 5% reduction in mortality in the enteral group. Two interim analyses were planned after 1,000 and 2,000 patients. The data safety and monitoring board had access to unblinded results on mortality, SOFA scores, bilirubin values and acquired infections and communicated to the investigators only if the trial should continue or stop. All statistical analysis was performed with the intention-to-treat approach.

After the second interim analysis the trial for stopped on the recommendation of the safety and monitoring board, as recruitment completion was deemed unlikely to change the results. Over a two-year period up to the trial cessation, a total of 10,855 patients were screened. There were 5,995 patients who met exclusion criteria, with the majority

due to treatment limitations (47%) or recent gastrointestinal surgery (25%). 2,450 patients were eligible, but not recruited. 2,410 patients were recruited, 1,202 to the enteral group and 1,208 to the parenteral group. Baseline characteristics were similar; patients were around 66 years old, mainly male (67%) with almost three quarters suffering from a pre existing illness. The majority of patients were medical (93%), almost two thirds had sepsis and half presented with acute respiratory failure. The mean SOFA score in both groups was 11. The majority of patients were sedated, with 30% administered neuromuscular blocking drugs. Noradrenaline was used most frequently for haemodynamic support at a dose around 0.5 µg/kg/min. Gastric ulcer prophylaxis was given to 42% of patients while prokinetic use was low (2%). 40% of patients required insulin.

The median time to randomisation was 16 hrs in both groups. Parenteral nutrition was delivered for a median of 4 days in the parental group, while the enteral groups received enteral nutrition for a median of 6 days. There was little cross over with only 4% of the parenteral group receiving enteral in the first 72 hrs and only 6% of the enteral group receiving parenteral nutrition in the first week. The daily calorie intake approached the 20 kcal/kg per day target in both groups. However, the parenteral group had a higher daily calorie intake (19.6 kcal/kg vs. 17.8 kcal/kg;  $P < 0.0001$ ) and protein intake (0.8 g/kg vs. 0.7 g/kg;  $P < 0.0001$ ) and a lower frequency of hypoglycaemia (29 vs 13;  $P < 0.0001$ ). Patients in the enteral group had higher rates of vomiting (333 vs. 158;  $P < 0.0001$ ) and were more frequently prescribed prokinetic medication (352 vs. 130;  $P < 0.0001$ ).

In terms of the primary outcome, by day 28, 443 (37%) of 1,202 patients in the enteral group and 422 (35%) of 1,208 patients in the parenteral group had died (absolute difference estimate, 2.0%; 95% CI, -1.9 to 5.8;  $P = 0.33$ ). In terms of secondary outcomes, there were no differences in 90 day, ICU, or hospital mortality; days without mechanical ventilation, vasopressor support, or renal replacement therapy. Length of ICU and acute hospital stays were similar. There were no differences in the frequency of any infections. Gastrointestinal complications were more frequent in the enteral group; specifically, vomiting (406 vs. 246;  $P < 0.0001$ ), diarrhoea (432 vs. 393;  $P = 0.009$ ), bowel ischaemia (19 vs. 5;  $P = 0.007$ ) and pseudo obstruction (11 vs. 3;  $p=0.04$ ).

## Critique

The NUTRIREA-2 trial is the second large randomised trial investigating the effect of the route of nutritional support in critical illness. The similar CALORIES trial was published during the recruitment period for NUTRIREA-2.<sup>9</sup> Both trials compared parenteral with enteral nutrition in largely medical critically ill patients and therefore neither address nutritional supplementation in surgical patients. Furthermore, neither trial incorporated nutritional risk screening which has been recommended.<sup>3</sup> Critically ill, malnourished

patients may benefit most from nutritional supplementation.<sup>10</sup> In contrast to the CALORIES trial, the NUTRIREA-2 trial specifically recruited patients who were ventilated and required vasopressors for haemodynamic support. This resulted in a population with higher SOFA scores than the CALORIES trial. Of particular note, the patients in NUTRIREA-2 required a high median dose of noradrenaline (approx. 0.5mcg/kg/min).

Guidelines suggest caution when implementing enteral nutrition in haemodynamically unstable patients, but recommend early introduction within either 24 or 48 hours of admission.<sup>3,11</sup> Nutrition in both groups was commenced within 16 hours of intubation, when perhaps resuscitation was still in progress and high doses of vasopressors were clearly required. Timing of nutrition may be important, with early introduction of enteral nutrition associated with better outcomes, and also some evidence to suggest that the patients who benefit most are those who are vasopressor dependent.<sup>4,12</sup> Therefore, despite some divergence from recommendations, by implementing enteral nutrition early in unstable patients the investigators attempted to, justifiably, optimise the conditions that might show a superiority of enteral over parenteral nutrition.

Despite these efforts, the trial failed to demonstrate a significant difference in the primary outcome of 28-day mortality, a result consistent with previous meta analyses.<sup>3,7,13</sup> Guidelines recommend early enteral nutrition rather than parenteral because of a reported reduction in new infections, although why exactly this fails to equate into a mortality difference is unclear.<sup>3,14</sup> In stark contrast to the results of these meta analyses and guidelines the NUTRIREA-2 trial did not demonstrate a difference in infective complications. These results are coherent with the results of the CALORIES trial, which also failed to show a benefit with enteral nutrition.<sup>9</sup> These findings may be due to improvements in the management of central venous access or infection control policies and thus a reduction in the risk of parenteral administration.

A further explanation could relate to the dose of nutrition administered. A criticism of parenteral nutrition has been the risk of overfeeding leading to harm.<sup>1</sup> Additionally hypocaloric feeding has been associated with either no difference in outcome or associated with potential benefits in terms of less infections, shorter ventilation and length of stay.<sup>15,16</sup> Recommendations suggest an intake of 20-25 kcal/kg/day in the acute phase of critical illness.<sup>8,11</sup> The NUTRIREA-2 trial failed to achieve these targets in either group. However the administered doses (19.6 kcal/kg/day in the parenteral vs 17.8 kcal/kg/day in the enteral group) were higher than the CALORIES trial and close to recommended intakes. It is likely the difference between the groups is probably not clinically significant. This is a testament to conduct of the study and the management of the enteral nutrition arm.

As well as provision of calories, protein administration is also important. Although critical illness is associated with increased proteolysis<sup>1</sup>, protein requirements during critical illness are not known, with previous protein augmenting studies producing conflicting results.<sup>19,20</sup> Protein intake was similar between groups (0.8 g/kg/day in the parenteral vs. 0.7 g/kg/day in the enteral group), but significantly lower than recommended doses of 1.2 to 2 g/kg/day.<sup>3</sup>

Finally, although the trial did not demonstrate a benefit of enteral or parenteral in terms of mortality, infections or length of stay, it may be logical to assume the the enteral route would remain the obvious choice to delivery nutrition, as this is non-invasive, cheaper and easier to administer. Yet, the NUTRIREA-2 trial provides new cautionary evidence against early enteral nutrition due to gastrointestinal complications. The rates of vomiting, diarrhoea and psuedo-obstruction were statistically higher, but most alarming was the four-fold increase in bowel ischaemia (5 patients in the parenteral group vs. 19 patients in the enteral group,  $P = 0.007$ ). Bowel ischaemia has been reported as a rare complication of enteral feeding but can be devastating and life ending.<sup>3</sup> Consistent with this finding, the CALORIES trial also reported higher rates of gastrointestinal complications.<sup>9</sup> Patients in CALORIES were less severely ill, had lower doses of nutrition administered and the intervention was commenced later, which could explain why there was no observed difference in bowel ischaemia. Perhaps the recommendations, mainly based on expert opinion, were correct that in haemodynamically unstable patients delaying enteral nutrition until stable and vasopressors are weaning is the better option. Unfortunately the question whether to use parenteral, avoid nutrition altogether or perhaps use deliberate hypocaloric nutrition in these patients remains unanswered. Perhaps additional groups in the NUTRIREA-2 trial might have addressed these questions and not left us hungry for more answers. *(Chris Nutt wrote this and the other authors wish to dissociate themselves from this remark).*

### **Where this sits in the body of evidence**

In the CALORIES trial, 2,388 patients were randomised to parenteral ( $n = 1,191$ ) or enteral ( $n = 1,197$ ) nutrition, commenced within 36 hrs of ICU admission and continued for 5 days.<sup>9</sup> Nutritional targets were set at 25 kcal/kg/day. The primary outcome was mortality at 30 days. Neither group met nutritional targets. Overall mortality was 33.1% in the parenteral group and 34.2% in the enteral group (relative risk in parenteral group, 0.97; 95% CI, 0.86 to 1.08;  $P = 0.57$ ). Hypoglycemia was less frequent in the parental nutrition group (3.7% vs. 6.2%;  $P = 0.006$ ), as was vomiting (8.4% vs. 16.2%;  $P < 0.001$ ). There were no differences in infectious complications or other outcomes.

In a randomised multi-centre controlled trial of early (within 48 hrs) versus delayed (after 8 days) initiation of supplemental parenteral nutrition, 2,312 patients received early parenteral while 2,328 patients had delayed parenteral nutrition.<sup>13</sup> All patients had a protocol for the early initiation of enteral nutrition. Patients in the parenteral group received significantly more calories for the first seven days. The primary outcome of length of ICU stay was one day shorter in the delayed parenteral group, 3 days (2-7) vs 4 days (2-9)  $P = 0.02$ . Patients in the late-initiation group, as compared with the early-initiation group, had fewer ICU infections (22.8% vs. 26.2%,  $P = 0.008$ ) although ICU, hospital and 90-day mortality were similar. In a post hoc analysis of early versus late nutrition in a population with relative contraindication to enteral nutrition, the infection reduction in the hypocaloric group was more significant 29.9% versus 40.2%,  $P = 0.01$ .

In a multi-center, randomised, single-blind clinical trial in 31 intensive care units, 1,372 patients were allocated to standard care ( $n = 686$ ) or to early parenteral nutrition ( $n = 686$ ).<sup>17</sup> In the standard care group, 199 patients (29.2%) initially commenced EN, 186 patients (27.3%) commenced PN, and 278 patients (40.8%) remained unfed. Day-60 mortality did not differ significantly (22.8% for standard care vs. 21.5% for early PN; risk difference, -1.26%; 95% CI, -6.6 to 4.1;  $P = 0.60$ ). However, early PN patients required fewer days of invasive ventilation (7.73 vs 7.26 days per 10 patient  $\times$  ICU days, risk difference, -0.47; 95% CI, -0.82 to -0.11;  $P = 0.01$ ), but this did not translate to shorter ICU or hospital length of stay.

In a randomised controlled trial 305 critically ill patients who had received less than 60% calorific requirements from enteral nutrition after 72 hrs were assigned to either continue with enteral nutrition or enteral supplemented with parenteral nutrition up to 100% of calculated requirements.<sup>18</sup> Energy targets were calculated with indirect calorimetry if possible or set at 25-30 kcal/kg/day. Mean energy delivery between day 4 and 8 was 28 kcal/kg/day for the PN group compared with 20 kcal/kg/day for the EN group. Up to day 28, 41 (27%) of 153 patients in the SPN group had a nosocomial infection compared with 58 (38%) of 152 patients in the EN group (hazard ratio, 0.65; 95% CI, 0.43-0.97;  $P = 0.0338$ ).

### **Should we routinely choose initial parenteral rather than enteral nutrition in haemodynamically unstable critically ill patients?**

Possibly. Although parenteral nutrition offers no survival benefit over enteral nutrition in this setting, its use results in less gastrointestinal complications, a finding seen in two major randomised controlled trials

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# Haematology Trials





## TRANSFUSE

**Cooper DJ, McQuilten ZK, Nichol A, Ady B, Aubron C, Bailey M et al. Age of Red Cells for Transfusion and Outcomes in Critically Ill Adults. *N Engl J Med* 2017;377:1858-1867**

### Introduction

Anaemia is a common occurrence in critically ill patients, with up to 97% becoming anaemic by day 8.<sup>1</sup> In the absence of signs and symptoms of anaemia or acute coronary syndrome, several multi-centre randomised controlled trials have demonstrated no difference in outcome whether a restrictive or liberal transfusion policy is implemented.<sup>2-4</sup> Presently, allogeneic, packed red cell transfusion is the mainstay of treatment for anaemia in ICU.<sup>5</sup>

Whilst packed red cells can be stored for up to 42 days in blood bank, it is recognised they undergo biochemical and structural changes whilst in storage which may be associated with harm.<sup>6</sup> Usual practice is for blood banks to issue the oldest units of packed cells for transfusion to ensure this valuable resource is utilised most efficiently.<sup>7</sup>

The recently published ABLE and RECESS trials demonstrated no difference in 90 day mortality or in organ dysfunction when fresher red cells were transfused in comparison to standard issue older red cell units.<sup>8,9</sup> This reassures us our current practice is safe. The ABLE trial had, however, a relatively small number of patients and RECESS looked specifically at post-cardiac surgical patients.

TRANSFUSE is a larger randomised controlled trial which aimed to further evaluate the effect of transfusion of the freshest available red cells against standard issue red cells.

### Synopsis

The Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) lead the design and implementation of this multi-centre, double-blind, randomised, controlled trial involving 59 centres across 5 countries. The investigators hypothesised that transfusion of the freshest available leuco-reduced, allogeneic, packed red cells (short-term group) would reduce all-cause 90-day mortality, compared to transfusion of the oldest available packed red cells (long-term group).

Adult patients admitted to the ICU, predicted to stay more than 24 hours, and in whom clinical staff had decided to transfuse with red cells, were eligible for recruitment. Among the exclusion criteria were those with a previous transfusion, haematological malignancy, cardiac surgical and organ transplantation patients.

Treating physicians determined the need for transfusion, timing and number of red cells to be transfused. Participating centres were encouraged to utilise a haemoglobin transfusion trigger of 70 g/L in the absence of acute coronary syndrome or clinical signs and symptoms of anaemia. All red cell packs were leuco-reduced and resuspended in saline-adenine-glucose-mannitol. The shelf-life for packed red cells in participating centres was either 35 days or 42 days.

Eligible patients were randomised via a web-based computer system, in a 1:1 ratio using blocks of variable sizes, stratified by centre. Randomisation resulted in a unique identification number being assigned to each patient. This unique identification number was then used by laboratory staff to assign patients to the appropriate treatment group. Clinical staff were blinded to the collection and expiration dates on the red cell units, using either opaque stickers or a bag with opaque panels. Randomised patients continued to receive red cells according to the group into which they were allocated for the duration of their hospital stay, as per their unique identification number.

The primary outcome was all-cause 90-day mortality. Secondary outcomes included 28-day mortality, ICU and hospital length of stay, days alive and free from mechanical ventilation at day 28, days alive and free from renal replacement therapy (RRT) at day 28 and incidence of febrile non-haemolytic transfusion reactions.

Accounting for loss to follow-up, a planned enrolment of 5,000 patients was required to detect an absolute risk reduction of 4.2% (relative risk reduction 15%) in 90 day all-cause mortality, from a baseline of 28%, with a power of 90% at a two-sided significance level of 0.05. Data analysis was by intention-to-treat.

Of 6,353 patients initially assessed, 4,994 underwent randomisation (2,490 to the short-term group and 2,504 to the long-term group). 1,280 patients were overlooked by clinical staff for randomisation, accounting for the majority of those excluded. After withdrawal of consent and loss to follow-up of patients in both groups, 2,457 and 2,462 patients were analysed for 90-day mortality in the short-term and long-term groups, respectively.

Patients in the short-term group were slightly older than those in the long-term group,  $62.5 \pm 16.8$  vs.  $61.4 \pm 17.3$  years, respectively. The groups were otherwise well matched at baseline. 52.2% (n=2,569) of patients were male. It is unclear how recruited patients were split between medical vs. surgical specialities and emergency vs. elective cases. The primary diagnosis was classified according to APACHE III-J diagnostic code - 21.7% (n=1,065) of patients were suffering from a primary gastrointestinal condition on admission, 16.4% (n=809) were admitted with sepsis and 10.2% (n=502) trauma. The

median SOFA score at baseline was 7 in each group. 50.5% (n=2,486) of patients were mechanically ventilated at baseline and 14.3% (n=702) were receiving RRT.

The mean haemoglobin level pre-transfusion was  $74.4 \pm 9.8$  g/L vs.  $74.3 \pm 10.2$  g/L in the short and long-term groups, respectively. Groups separated well with regard to duration of storage of transfused red cells;  $11.8 \pm 5.3$  days vs.  $22.4 \pm 7.5$  days, in the short vs. long-term groups, respectively. The mean number of units transfused was  $4.1 \pm 6.0$  in the short-term group vs.  $4.0 \pm 6.2$  in the long-term group.

There was no difference between groups in the primary outcome of 90-day mortality - 24.8% (n=610) in the short-term group vs. 24.1% (n=594) in the long-term group (unadjusted OR, 1.04; 95% CI, 0.91 to 1.18; P = 0.57). Febrile non-haemolytic transfusion reactions were more frequent among the short-term storage group than the long-term storage group, 5.0% (123 events) vs. 3.6% (88 events) (unadjusted OR, 1.42; 95% CI 1.07 to 1.88; P = 0.01). Otherwise, no difference in any of the secondary outcomes was elicited.

Pre-specified subgroup analysis revealed a higher mortality with fresh red cell transfusion among patients with an APACHE III predicted risk of death at hospital discharge above the median of 21.5% (OR 1.18; 95% CI, 1.00 to 1.39; P = 0.05). Mortality did not differ between patients who exclusively received red cells stored for less than 8 days (n=420) compared to patients who received only red cells stored for more than 35 days (n=143).

## Critique

This is the largest RCT to date, which examines the question of how age of transfused red cells affects outcome in the critically ill. The results of TRANSFUSE re-affirm the findings of ABLE and RECESS which were published in 2015.<sup>8,9</sup>

As RECESS looked specifically at a post-cardiac surgical population, important comparisons can be more easily drawn between TRANSFUSE and ABLE (Table 13). Both of these trials measured the same primary outcome, 90-day all-cause mortality, in a more general sample of ICU patients. The mean APACHE II score in ABLE was 21.8 whilst patients recruited to TRANSFUSE had a mean APACHE III score of 72.9. Whilst the APACHE II and APACHE III scores are not directly comparable, it appears ABLE recruited sicker patients than TRANSFUSE (Table 13). ABLE also recruited exclusively from tertiary level ICUs which was not the case in TRANSFUSE.

Patient Characteristics	TRANSFUSE	ABLE
Number randomised	4,994	2,510
Baseline organ support	50% mechanical ventilation 14% RRT	98% mechanical ventilation 28% RRT
Absolute difference in duration of red cell storage between study groups (days)	10.6	15.9
Mean no. of units transfused	4.1	4.3
Mean time from randomisation to transfusion (hours)	1.5	10
Median ICU LOS (days)	4	15
Median hospital LOS (days)	14	34
90-day mortality	24.4% Short-term group 24.1% Long-term group	37% Fresh blood 35.3% Standard blood

**Table 13. Comparison of TRANSFUSE and ABLE trials**

*RRT = renal replacement therapy; LOS = length of stay*

The mean duration of red cell storage in the long-term group in TRANSFUSE was 22±7.5 days compared to 22±8.4 days in the standard group of ABLE. The threshold duration of storage which would result in blood becoming harmful remains uncertain. With only 143 patients in TRANSFUSE receiving blood of > 35 days duration, the question of whether old blood is harmful remains somewhat unanswered. Although a secondary outcome measure, febrile non-haemolytic reactions were more frequently seen in the short-term storage group.

The mean number of red cells transfused was almost identical between trials (4 units) and thus the dose of red cells required to cause harm again remains uncertain. Looking at the mean Hb level prior to transfusion across the study groups in both trials, it is interesting to note how transfusion practices in Canada and Europe where ABLE was undertaken seems to be similar to Australia and New Zealand where the majority of patients for TRANSFUSE were recruited. It would appear that the ICU community has embraced the evidence for restrictive transfusion strategies as per the TRICC, TRISS and TITRe2 studies.<sup>2-4</sup>

The strengths of TRANSFUSE lie in the numbers of patients recruited, the blinding of clinical and research staff and the short time from randomisation to transfusion (median 1.5 hours (IQR 0.8-2.7hrs), thus minimising the risk of harm to patients arising from delayed transfusion.

We should be reassured our current practice of issuing and transfusing packed cells which have been stored longest in our blood banks is safe.

### **Where this sits in the body of evidence**

The ABLE trial randomised patients to receive RBCs less than 8 days old or the oldest compatible RBCs available in blood bank.<sup>8</sup> The mean age of transfused blood was  $6.1 \pm 4.9$  days in the fresh blood group versus  $22.0 \pm 8.4$  days in the standard issue blood group ( $P < 0.001$ ). There was no difference between the two groups in the primary outcome measure of 90-day mortality; 37.0% in the fresh-blood group versus 35.3% in the standard-blood group (absolute risk reduction, 1.7%; 95% CI, -2.1 to 5.5).

The RECESS study also examined the effect of age of transfused RBC, comparing blood stored for 10 days or less (shorter-term storage group) with that stored for 21 days or more (longer-term storage group) in patients 12 years or older undergoing complex cardiac surgery.<sup>9</sup> There was no difference in the primary outcome measure of change in Multiple Organ Dysfunction Score; a mean increase of 8.5 points was seen in the shorter-term storage group compared to 8.7 points in the longer-term storage group (95% CI for the difference, -0.6 - 0.3;  $P = 0.44$ ). There was no difference in 7 day or 28 day mortality.

In a double-blind trial, Fergusson and colleagues randomised 377 premature infants with birth weights less than 1250 g to receive either RBC less than 7 days old or standard issue RBCs. The primary outcome measure was a composite of necrotising enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, intraventricular haemorrhage and death. The primary outcome measure occurred in 52.7% of the fresh RBC group compared with 52.9% of the standard RBC group. There was no difference in infectious complications.<sup>10</sup>

A large Scandinavian cohort study, involving 404,959 transfusion episodes, demonstrated a 5% increase in mortality in patients who received RBC stored for between 30 - 42 days. This effect persisted from 7 days to two years.<sup>11</sup>

In a retrospective study of 6002 cardiac surgical patients, patients who had received RBC that had been stored for greater than 14 days were compared to those who had received RBC that had been stored for less than 14 days. The groups were unevenly balanced in some regards. Logistic regression analysis and propensity score matching was used to

adjust for these imbalances. A composite end point of complications was more likely in those who received older blood (25.9% vs. 22.4%,  $P = 0.001$ ). Patients who received the older blood also had a higher in hospital mortality (2.8% vs. 1.7%,  $P = 0.004$ ) and 1 year mortality (7.4% vs. 11.0%,  $P < 0.001$ ). The investigators concluded that administration of RBC less than 14 days of age would prevent one additional death for every 28 patients treated.<sup>12</sup>

In an observational study of 11,963 patients who underwent coronary artery bypass grafting, 5,184 of whom were transfused in the perioperative period, the use of RBC was associated with an increase in mortality. The adjusted odds ratio for death in those who received RBC compared to those who did not was 1.77 (95% CI, 1.67 - 1.87;  $P = 0.0001$ )<sup>13</sup>

The TRICC study enrolled 838 critically ill but euvolaemic patients. These patients were randomised to either a restrictive transfusion strategy (a transfusion trigger of 70 g/L with a target maintenance hemoglobin 70 - 90 g/L) or a liberal transfusion strategy (a transfusion trigger of 100 g/L with a target maintenance haemoglobin 100 - 120 g/L). There was no difference in 30 day mortality between the two groups (18.7% in the restrictive group vs. 23.3% in the liberal group,  $P = 0.11$ ).<sup>2</sup>

The TRISS study examined the role of restrictive and liberal transfusion thresholds in critical ill patients with septic shock. Transfusion thresholds were similar to the TRICC study. There was no difference in the primary endpoint of 90 day mortality; 43.0% in patients assigned to the lower transfusion threshold group died, as compared with 45.0% of patients assigned to the higher transfusion threshold group (relative risk, 0.94; 95% CI, 0.78 - 1.09;  $P = 0.44$ )<sup>4</sup>

The TITRe2 trial examined the impact of using a restrictive transfusion threshold (threshold for transfusion 75 g/L) compared to a liberal transfusion threshold (threshold for transfusion 90 g/L) in patients following cardiac surgery. Transfusion rates were much lower in the restrictive transfusion threshold group compared to the liberal transfusion threshold group (53.4% vs. 92.2%). The primary endpoint was a composite of serious infection or an ischaemic event (permanent stroke, myocardial infarction, infarction of the gut, or acute kidney injury) at 3 months. A total of 2007 patients were enrolled. The primary outcome measure occurred in 35.1% of the patients in the restrictive threshold group and 33.0% of the liberal threshold group (OR, 1.11; 95% CI, 0.91 to 1.34;  $P = 0.30$ ).<sup>3</sup>

### **Should we change from current practice of using the oldest available blood in blood bank?**

No. TRANSFUSE provides reassurance that current practice is safe.

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## TRICOP

**Bergamin F, Almeida J, Landoni G, Galas F, Fukushima J, Fominskiy E, et al. Liberal Versus Restrictive Transfusion Strategy in Critically Ill Oncologic Patients: The Transfusion Requirements in Critically Ill Oncologic Patients Randomised Controlled Trial. Crit Care Med 2017;45(5):766-773**

### Introduction

A restrictive transfusion policy is as safe and effective as a more liberal transfusion policy in general ICU patients, as well as in sub-groups such as cardiac surgical, gastrointestinal haemorrhage and septic shock.<sup>1-4</sup> Other subgroups may, however, be at increased risk of harm from a restrictive transfusion policy. In cancer patients admitted to critical care post-operatively, a restrictive transfusion policy was associated with a two-fold increase in mortality and major morbidity.<sup>5</sup>

There is a sparsity of high quality evidence to guide transfusion strategies in the critically ill septic patient. A recent meta-analysis concluded a restrictive strategy in septic patients was safe.<sup>6</sup> Transfusion was associated, however, with a higher incidence of nosocomial infection, acute lung injury and acute kidney injury in these patients. This meta-analysis contained only one randomised, controlled trial and 12 cohort studies, with substantial heterogeneity between studies.

Many large multi-centre, randomised-controlled trials exclude patients with cancer, but it is estimated 15% of patients admitted to ICU with sepsis have an underlying neoplastic process.<sup>7</sup> Although 7.5% of patients recruited to the TRISS trial were suffering from a haematological malignancy, the number of patients with solid tumours in the TRISS trial was unknown.<sup>4</sup>

How does a restrictive transfusion policy influence the outcome of cancer patients admitted with sepsis? Is a liberal transfusion strategy in these patients harmful? The TRICOP trial was designed to answer these questions.

### Synopsis

The hypothesis behind this single centred, randomised controlled trial was that a restrictive transfusion strategy (haemoglobin threshold < 70 g/L) would reduce the 28-day mortality of patients admitted to the intensive care unit with a solid tumour and suffering from septic shock, compared to a more liberal transfusion strategy (haemoglobin threshold < 90 g/L). It was conducted at a tertiary referral oncology centre in Sao Paulo, Brazil.



The definition of septic shock used was that of proven or suspected infection in a patient who had a MAP < 65 mm Hg, despite fluid resuscitation and therefore requiring vasopressor support.

The 28-day mortality rate for cancer patients suffering from septic shock was estimated to be 50%. The power calculation was based on an estimation that a restrictive transfusion policy would reduce 28-day mortality in this cohort of patients by 16%. At 80% power and a 5% significance level, a sample size of 300 patients was required to detect such a difference, if one existed. Data was analysed according to the intention-to-treat principle.

1,658 adult patients (> 18 years of age) admitted to the ICU were assessed for eligibility, with 82% of these (n = 1,358) excluded. The greatest proportion of patients (n = 407) were excluded as they were suffering from a haematological malignancy rather than a solid tumour. Three hundred patients were randomised within 6 hours of ICU admission; 149 to the liberal group and 151 to the restrictive group. There were no patients lost to follow-up.

The primary outcome measure was 28-day all-cause mortality. Among the secondary outcomes were the need for mechanical ventilation, inotropic support and renal replacement therapy. ICU and hospital length of stay, together with 60- and 90- day mortality were also among the secondary outcome measures of interest.

The intervention period only applied whilst the patient was in the ICU. The clinical team caring for these patients were aware of study group allocations and they decided when to transfuse. The decision to transfuse was therefore unblinded. Patients and the three investigators who collected the outcome data were blinded.

Patients had haemoglobin measured on ICU admission and twice per day thereafter. If the haemoglobin dropped below the given threshold in either group a transfusion of leucodepleted RBCs was given. A single unit of RBCs was transfused at a time, with haemoglobin measured after each RBC transfusion.

51% (n = 154) of patients were male with a mean age of 61.5 ( $\pm$  13.2) years. Patients were well matched at baseline in terms of co-morbidities. The commonest tumour type was gastrointestinal 56% (n = 167). The majority of patients were suffering from a respiratory source of infection 65% (n = 194). Although transfusion rates prior to ICU admission were not disclosed, the admission haemoglobin levels were well matched between groups, 97 g/L ( $\pm$  21) vs. 96 g/L ( $\pm$  21) in the liberal vs. restrictive groups, respectively.

61% (n = 91) of patients in the liberal group were transfused compared to 41% (n = 62) in the restrictive group. Overall, the lowest daily haemoglobin concentration was significantly higher in the liberal group compared to the restrictive group (a difference of approximately 7.0 g/L; P = 0.038). Considering only transfused patients, the lowest haemoglobin concentration was also significantly higher in the liberal group (a difference of approximately 10 to 15 g/L; P < 0.001). The total number of red cells transfused was higher in the liberal group (314 vs. 212). Median age of transfused red cells was not significantly different between groups; 9 (6 to 2) vs. 8 (5-to 10) days in the liberal vs. restrictive groups, respectively (P = 0.07). There were few protocol violations, 3% of patients in the liberal group vs. 5% of patients in the restrictive group.

The 28-day mortality was 45% (n = 67) vs. 55.6% (n = 84) in the liberal vs. restrictive groups, respectively (OR, 0.74; 95% CI, 0.53 to 1.04; P = 0.08). This non-statistically significant difference for reduced mortality persisted at 60 days, 56.4% vs. 65.6% (OR, 0.77; 95% CI, 0.55 to 1.07; P = 0.12), but became significant at 90 days post-randomisation, 59.1% vs. 70.2% (OR, 0.72; 95% CI, 0.53 to 0.97; P=0.03), in the liberal vs. restrictive groups, respectively. These were, however, secondary outcomes and should be regarded as hypothesis generating only (the fragility index for the 90 day mortality was 1).

There were no differences in any of the remaining secondary outcomes, including (liberal strategy vs. restrictive strategy) need for mechanical ventilation (30.9% vs. 38.7%; OR, 0.71; 95% CI 0.44 to 1.15; P = 0.160), need for renal replacement therapy (8.7% vs. 12.0%; OR, 0.70; 95% CI 0.33 to 1.49; P = 0.35), need for inotropic support (16.2 vs. 22.1%; OR, 0.68; 95% CI 0.38 to 1.22; P = 0.19), acute myocardial infarction (2.7% vs. 2.7%; OR, 1.00; 95% CI, 0.25 to 4.00; P = 1.00) or any other form of ischaemia. There were no between-group differences in ICU- or hospital- length-of-stay, at approximately 1 and 2 weeks, respectively.

## Critique

The TRICC trial suffered from a low representation of septic shock patients (only 25% of included patients had infection), while the TRISS trial lacked representation of cancer patients (7.5% had a haematological malignancy).<sup>1,4</sup> How a restrictive transfusion policy impacted on the outcome of a specific subgroup of ICU patients, namely those suffering from a solid organ tumour with septic shock was unknown. This trial is therefore an important addition to the growing evidence base of transfusion practices in ICU.

The investigators report a potential signal of harm from the restrictive transfusion policy in this patient population, with a non-significant improvement in 28-day mortality among the liberal transfusion group. This was an unexpected finding. Perhaps in cancer

patients with septic shock, anaemia is more deleterious than in the general ICU population. Although secondary outcomes, there were no significant difference in the rates of myocardial, limb and cerebral ischaemia between the groups.

This study was conducted in a tertiary referral oncology centre. Baseline characteristics of the included patients deserves some discussion. Although this study included only cancer patients with solid organ tumours, this sub-group itself is quite a heterogenous population – not all cancers are the same. The proportion of patients with metastases is unclear. How the patients were divided between medical and surgical admissions is also not clear from the main text or the supplementary material. Were the surgical patients in this study emergency surgical patients or elective patients? Did surgical patients in this study undergo a period of pre-operative optimization in the form of iron supplementation or erythropoietin injections? Was intraoperative cell salvage used in many cases? All of these factors, in addition to a transfusion policy, may impact upon post-surgical transfusion rates.

The investigators, in the power calculation, estimated a restrictive transfusion policy in septic cancer patients would result in a 16% absolute reduction in mortality. The number of patients transfused in the restrictive group was, in fact, 29 less than in the liberal group (62 vs. 91 respectively). Given this was a single centred study containing only 300 patients the estimation of mortality effect used in the power calculation seems grossly over optimistic.

The definition of septic shock used is quite non-specific. Although 100% of patients included in the study are labelled as having cardiovascular dysfunction, the mean volume of IV fluid infused prior to randomisation, and the mean dose of vasopressor administered is unknown. The mean baseline serum lactate in either group is not given. This begs the question as to the degree of septic shock these patients were suffering on admission.

The median SOFA score for each group in the TRISS study was 10 (8-12), with approximately 70% of patients requiring mechanical ventilation.<sup>4</sup> In this study, the median SOFA score was 7 (5 to 9) with only 35% (n = 104) requiring mechanical ventilation, implying the patients included in this study were not as unwell as those in the TRISS. The low requirement for mechanical ventilation is surprising, given that in 64% (n = 194) of cases the primary source of infection was felt to be the lung.

This was a pragmatic study where blinding of healthcare staff caring for patients was not possible. There was clear separation between the groups in terms of the lowest daily haemoglobin concentration and the number of red cells transfused, with few protocol

violations. This trial therefore demonstrates how it is possible to implement and adhere to a given transfusion strategy in ICU for cancer patients suffering from septic shock and thus can serve as a template for a larger multi-centre trial in the future. However, as a single centre study in a specialized hospital, this trial will need to be repeated as a multi-centre, randomised controlled trial in order to clarify these results.

### **Where this sits in the body of evidence**

The TRICC study randomised 838 critically ill euvoelaemic patients to either a restrictive transfusion strategy (a transfusion trigger of 70 g/L, with a target maintenance haemoglobin 70 - 90 g/L) or a liberal transfusion strategy (a transfusion trigger of 100 g/L with a target maintenance haemoglobin 100 - 120 g/L).<sup>1</sup> There was no difference in 30-day mortality between the two groups (18.7% in the restrictive group vs. 23.3% in the liberal group;  $P = 0.11$ ).

The TRISS study examined the role of restrictive and liberal transfusion thresholds in critically ill patients with septic shock. Transfusion thresholds were similar to the TRICC trial.<sup>4</sup> There was no difference in the primary endpoint of 90-day mortality; 43.0% in patients assigned to the lower transfusion threshold group died and 45.0% of patients assigned to the higher transfusion threshold group (relative risk, 0.94; 95% CI, 0.78 - 1.09;  $P = 0.44$ ).

The TITRe2 trial examined the impact of using a restrictive transfusion threshold (threshold for transfusion 75 g/L) compared to a liberal transfusion threshold (threshold for transfusion 90 g/L) in patients following cardiac surgery.<sup>2</sup> Transfusion rates were much lower in the restrictive transfusion threshold group compared to the liberal transfusion threshold group (53.4% vs. 92.2%). The primary endpoint was a composite of serious infection or an ischemic event (stroke, myocardial infarction, infarction of the gut, or acute kidney injury) at 3 months. A total of 2,007 patients were enrolled. The primary outcome measure occurred in 35.1% of patients in the restrictive threshold group and 33.0% of the liberal threshold group (OR, 1.11; 95% CI, 0.91 to 1.34;  $P = 0.30$ ).

In a study of surgical abdominal oncology patients admitted post-operatively to ICU, Almeida et al randomised 198 patients to a liberal (transfusion if Hb < 90 g/L) versus a restrictive (transfusion if Hb < 70 g/L) strategy.<sup>5</sup> This parallel group, randomised controlled trial was carried out at the same centre as the TRICOP study, critiqued above. The rate of transfusion was significantly higher in the liberal group vs. restrictive group; 42.3% ( $n = 41$ ) vs. 20.8% ( $n = 21$ ), respectively. The primary outcome was a composite of mortality and severe morbidity within 30 days of randomisation and occurred in 19.6% ( $n = 19$ ) vs. 35.6% ( $n = 36$ ) in the liberal v restrictive groups, respectively ( $P = 0.012$ ).

In a single-centred Danish trial, 284 elderly patients admitted from a nursing home or sheltered accommodation with a hip fracture were randomised to a liberal (Hb < 113 g/L) or a restrictive (Hb < 97 g/L) transfusion policy.<sup>8</sup> Patients could be recruited up to 6 days post-operatively. The primary outcome measure was recovery from physical disability as measured by 3 tools of physical performance: Modified Barthel Index, New Mobility Score and Cumulated Ambulation Score. No difference in recovery from physical disabilities between the transfusion strategies was observed. Whether a haemoglobin threshold of 97 g/L is truly restrictive is debatable.

In an observational study of 11,963 patients who underwent coronary artery bypass grafting, 5,184 of whom were transfused in the perioperative period, the use of RBC was associated with an increase in mortality.<sup>9</sup> The adjusted odds ratio for death in those who received RBC compared to those who did not was 1.77 (95% CI, 1.67 to 1.87; P = 0.0001).

The single centre Brazilian non-inferiority TRACS trial randomised 502 consecutive adults undergoing cardiac surgery with cardiopulmonary bypass to two red cell transfusion thresholds, a liberal strategy targeting a haematocrit  $\geq$  30%, or a restrictive strategy, aiming to keep the haematocrit  $\geq$  24%.<sup>10</sup> The groups separated well with regards to both mean haemoglobin concentrations (105 vs. 91 g/L; P < 0.001) and number of patients receiving a red cells transfusion (78% vs. 48%; P < 0.001). There was no difference in the primary composite endpoint of 30-day all-cause mortality and in-hospital severe morbidity (non-inferiority margin -8%); liberal group, 10% vs. restrictive group, 11%; P = 0.085. There were no differences in secondary endpoints, including various organ-specific morbidities, ICU length of stay and hospital length of stay.

The multi-centre, open-label, non-inferiority (margin 3%) TRICS III trial randomised 5,243 adult cardiac surgical patients, at increased risk for death after cardiac surgery, to a restrictive red-cell transfusion threshold (hemoglobin <75 g/L) or a liberal red-cell transfusion threshold (haemoglobin < 95 g/L or < 85 g/L if outside ICU or theatre).<sup>11</sup> The primary outcome measure was a composite of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis and occurred in 11.4% of the restrictive group and 12.5% of the liberal group (absolute risk difference, -1.11%; 95% CI, -2.93 to 0.72; OR, 0.90; 95% CI, 0.76 to 1.07; P < 0.001 for noninferiority).

Koch and colleagues randomised 722 cardiac surgical patients to two transfusion thresholds, 24% haematocrit or 28% haematocrit.<sup>12</sup> The study was stopped after the second interim analysis for futility. Less patients in the lower threshold group received a red cell transfusion (54% vs. 75%, p < 0.0001). There was no difference in the primary composite outcome of in-hospital morbidity and mortality (lower threshold group, 16%

vs. higher threshold group, 19%; OR, 0.86; 95% CI, 0.29 to 2.54, P = 0.71). No treatment effect heterogeneity was observed across the composite outcome components.

The FOCUS trial randomised 2,016 hip fracture patients with cardiovascular disease, or risk factors for it, to either a restrictive transfusion strategy (physician option for transfusion if haemoglobin < 80 g/L) or liberal transfusion strategy (transfusion threshold 100 g/L).<sup>13</sup> The groups separated well in terms of red cell exposure, with the liberal group receiving a median of 2 units of red cells and the restrictive group a median of 0 units. There was no difference in the primary outcome of death or an inability to walk across a room without human assistance on 60-day follow-up; liberal-strategy group, 35.2% vs. restrictive-strategy group, 34.7%; (OR, 1.01; 95% CI, 0.84 to 1.22; absolute risk difference, 0.5%; 95% CI, -3.7 to 4.7). There were no differences in any secondary end-points, including in-hospital acute coronary syndrome (liberal-strategy group, 4.3% vs. restrictive-strategy group, 5.2%; absolute risk difference, -0.9%; 99% CI, -3.3 to 1.6).

### **Should we use a liberal strategy of red cell transfusion in critically ill solid tumour oncology patients with sepsis?**

Not at present. The body of evidence does not support the use of a liberal transfusion strategy. However, given the results of TRICOP a larger study of transfusion in critically ill patients with malignancy should be undertaken

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## RETIC

**Innerhofer P, Fries D, Mittermayr M, Innerhofer N, von Langen D, Hell T et al. Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. Lancet Haematol 2017;4:e258-71**

### Introduction

Trauma is a leading cause of death and disability in adults.<sup>1</sup> Uncontrolled post-traumatic bleeding is a major cause of potentially preventable death among injured patients, accounting for 30-40% of trauma-related mortality.<sup>2</sup> Traditionally, coagulopathy in trauma was attributed to blood and coagulation factor loss, with dilution during resuscitation confounded by acidosis and hypothermia. Although these factors contribute to bleeding, it is now recognised that an endogenous coagulopathy related to tissue injury can occur within minutes following injury.<sup>3</sup> Upon hospital admission one-third of all bleeding trauma patients already show signs of coagulopathy.<sup>4</sup> Furthermore, presence of early coagulopathy is associated with higher transfusion requirements, increased rates of multiple organ failure, longer intensive care unit stay and a fourfold higher mortality.<sup>4,5</sup>

Trauma-induced coagulopathy is a multifactorial condition that results from a combination of bleeding-induced shock, tissue injury related thrombin-thrombomodulin-complex generation, the activation of anticoagulant and fibrinolytic pathways, and platelet dysfunction.<sup>6</sup> Trauma management guidelines recommend early aggressive control of bleeding, limited fluid resuscitation until bleeding is controlled and monitoring for coagulopathy using either traditional laboratory or viscoelastic tests.<sup>7</sup> Tranexamic acid has become standard practice, however the continuing optimal management of detected or suspected trauma-induced coagulopathy remains uncertain. Guidelines recommend either fresh frozen plasma (FFP) or fibrinogen concentrates.<sup>7</sup> Fibrinogen is required for fibrin production and clot formation and is also integral to platelet aggregation. Fibrinogen concentrations decrease in trauma and are associated with poor outcomes.<sup>8,9</sup> The RETIC trial investigators hypothesised that early use of targeted coagulation factor concentrates (CFC) would more effectively increase clotting factors, reduce bleeding and transfusion requirements, and ultimately reduce multiple organ failure.

### Synopsis

RETIC was a single centre, randomised, unblinded trial performed at a level one trauma centre in Innsbruck, Austria. The aim was to compare the effects of CFC with FFP on the development of multi-organ failure in trauma-induced coagulopathy. On admission,



adult patients with blunt trauma, who had an Injury Severity Score (ISS) >15, and risk of, or clinical signs of, major haemorrhage, were screened for coagulopathy. Screening was performed using bedside rotational thromboelastometry (ROTEM). Patients were included if they met criteria for coagulopathy, which was defined as either low fibrinogen polymerisation (10-min value of fibrinogen polymerisation [FibA10] < 9 mm), or prolonged initiation of coagulation (coagulation time of ExTEM assay [ExCT] > 90 s). Patients were excluded if the injuries were considered unsurvivable, CPR was required at the scene, injuries sustained were isolated brain, burns or avalanche injury, or the patient had received coagulation products other than tranexamic acid prior to admission. Delayed presentation (> 6 hours), oral anticoagulants (including antiplatelet agents), history of thromboembolic events and pregnancy were the other main exclusions.

Eligible patients were randomised using a sealed envelope system with stratification depending on the presence of brain injury and injury severity using the ISS. Prior to the study intervention all patients received 20 mg/kg of tranexamic acid. Subsequently, patients received either fresh frozen plasma or coagulation factor concentrates immediately after randomisation and for up to 24 hours in the intensive care unit.

The intervention was delivered in treatment loops, which could be repeated up to 24 hours after ICU admission. Each treatment loop consisted of a maximum of two doses of study drug and either single or double dose rescue medication if required (Table 14). Bleeding was assessed using a bleeding score devised by the investigators:

- 0: no substantial bleeding
- 1: injury-related normal bleeding with visible clots
- 2: diffuse microvascular bleeding from wound and catheter insertion sites
- 3: massive bleeding with transfusion of > 3 units packed red cells per hour.

Successful treatment was defined as normalisation of the ROTEM and the absence of microvascular or massive bleeding after either one or two treatments. Treatment failure instigated the use of rescue therapy, which consisted of fresh frozen plasma in the coagulation factor group and coagulation factor concentrates in the FFP group.

The primary outcome was the occurrence of multiple organ failure during ICU admission, assessed using the SOFA score. Secondary outcomes were length of ICU and hospital stay, 24-hour and 30-day mortality, requirement for, and duration of, renal replacement therapy, ventilator-free days, and the occurrence of sepsis, infection and thromboembolic events. Transfusion requirements and results of coagulation tests were also recorded.

	CFC group		FFP group
	If abnormal fibrin polymerisation (FibA10 < 9 mm) on ROTEM	If delayed initial thrombin formation (ExCT >90 s or prothrombin time index [PTI] <35%)	
<b>1st dose<sup>a</sup></b>	Fibrinogen concentrate 50 mg/kg of bodyweight	PCC 20 IU/kg of bodyweight	FFP 15 mL/kg of bodyweight
<b>2nd dose<sup>b</sup></b>	Fibrinogen concentrate 50 mg/kg of bodyweight plus FXIII concentrate 20 IU/kg of bodyweight	PCC 20 IU/kg of bodyweight	FFP 15 mL/kg of bodyweight
<b>Rescue therapy<sup>b</sup></b>	FFP 15 - 30 mL/kg of bodyweight	FFP 15 - 30 mL/kg of bodyweight	Fibrinogen concentrate 50 - 100 mg/kg of bodyweight plus FXIII concentrate 20 - 40 IU/kg of bodyweight <i>or</i> PCC 20 - 40 IU/kg of bodyweight

**Table 14. The RETIC trial interventions**

<sup>a</sup> success defined as FibA10 >8 mm or ExCT <78 s and bleeding score 0–1).

<sup>b</sup> second dose or rescue therapy administered if ROTEM remained deranged and patient still demonstrating bleeding score 2-3 after previous trial drug administration

Based on a previous observational study with baseline multiple organ failure rates of 18% in the coagulation factor group and 37% in a group receiving both CFC and FFP, 200 patients were required to detect a significant difference in multi-organ failure rates, with a power of 80% and an alpha level of 0.05. An interim analysis was planned after 100 patients had been recruited. Analysis was performed using a modified intention-to-treat principle.

Over a four year period, a total of 292 patients were screened, 192 were ineligible (80% did not meet inclusion criteria) therefore 100 patients were randomised; FFP group, n = 48 vs. CFC group, n = 52. After the interim analysis, the trial was stopped early, as there was a significant difference in treatment failure and increased risk of massive transfusion in the FFP group. Six patients dropped out leaving 94 patients in this analysis.

Patients recruited were mainly male (74%), with a median age of 43 years (IQR 26 - 54) and an injury severity score of 34 (IQR 26 - 43). Almost half had a brain injury. Physiological parameters were similar between groups. The median systolic blood pressure was 106 mm Hg in the CFC group and 108 mm Hg in the FFP group. The FFP group had a lower heart rate, 93 vs. 103 bpm. Patients were mildly acidotic (pH 7.32, base deficit 4 mmol/L), with a marginal rise in lactate (2.2 mmol/L). The initial haemoglobin was approximately 120 g/L in both groups, while the prothrombin index was 68% in the CFC group and 65% in the FFP group. Fibrinogen levels were higher in the CFC group (197 vs. 177 mg/dL). ROTEM measurements were similar in both groups.

In terms of the intervention, the time until start of study medication was longer in the FFP group than in the CFC group {median 50.5 min (IQR 39.5 – 70.0) vs. 10 min (10 – 16);  $P < 0.0001$ }, as was time to correction of trauma-induced coagulopathy and normalisation of bleeding {128.0 min (48.3 – 186.3) vs. 22.5 min (13.5 - 40.0);  $P < 0.0001$ }. Correction of coagulopathy and bleeding was achieved with single dose of study drug in 12 patients (27%) in the FFP group and 38 patients (76%) in the CFC group. The odds in favour of successful treatment after single-dose study drug was higher for CFC than for FFP (OR 8.22; 95% CI, 3.1 to 23.8;  $P < 0.0001$ ). Nine patients (20%) in the FFP group and 10 patients (20%) in the CFC group needed double-dose administration, while rescue medication was necessary in 23 patients (52%) in the FFP group, but only in two patients (4%) in the CFC group. Persistent coagulopathy was primarily the reason for repeated or rescue treatment. The number needed to treat for reversal of coagulopathy with CFC only was 2.07 (95% CI, 1.6 to 3.1). Patients in the FFP group required more packed red cells (6 vs. 4;  $P = 0.03$ ) and were more likely to require a massive transfusion (30% vs. 12%; OR 3.04; 95% CI, 0.95 to 10.87;  $P = 0.042$ ).

The primary outcome of multiple organ failure occurred in 29 patients (66%) in the FFP group compared to 25 patients (50%) in the CFC group (OR 1.92; 95% CI, 0.78 to 4.86,  $P = 0.15$ ). In comparison to the CFC group, the FFP group had a higher mean ISS-adjusted SOFA score up to day 7 in ICU, and a longer duration of haemofiltration in the modified intention-to-treat analysis. There were no other significant differences in any clinical outcome measures. A post-hoc logistic regression analysis, adjusted for ISS and brain injury, showed an increased risk for multiple organ failure in the FFP group (OR 3.13;

95% CI, 1.19 to 8.88; P = 0.025). Post-hoc sub-group analysis based on rescue therapy showed a higher incidence of multiple organ failure in patients in the FFP with rescue group compared with the CFC only group (78% vs. 48%; OR, 3.84; 95% CI, 1.13 to 15.44; P = 0.021). There was no difference in rates of multiple organ failure between the FFP rescue and FFP only groups, respectively (OR, 0.31; 95% CI, 0.07 to 1.34; P = 0.11).

## Critique

Massive trauma is associated with derangements of haemostasis related to coagulation factor consumption, endogenous inhibition, resuscitative dilution with resultant poor clot formation, and pathological fibrinolysis with enhanced clot breakdown. Damage control resuscitation aims not only to maintain tissue oxygenation but also prevent clot breakdown and correct coagulopathy. This strategy has promoted the early use of blood products in ratios approximating whole blood (1:1:1 for units of plasma to platelets to red blood cells). However this approach has failed to show significant benefit over lower blood to plasma ratios.<sup>11</sup> Furthermore, the effectiveness of FFP has been questioned.<sup>10</sup>

Fibrinogen is the first coagulation factor to fall to suboptimal levels during bleeding. FFP contains approximately 2 g/L fibrinogen (around 0.6 g in a 300 ml unit) and therefore, in recommended doses, (15 ml/kg) may not adequately restore plasma fibrinogen levels.<sup>12,13</sup> Perhaps a criticism of the RETIC trial is that having identified a coagulopathy primarily due to hypofibrinogenaemia, that a higher initial dose of FFP was not administered. However, guidelines recommend either FFP or fibrinogen for trauma-induced coagulopathy.<sup>7</sup> In a single centre, open-label study, the RETIC trial demonstrated the use of thromboelastometry-guided CFC (mainly fibrinogen) improved coagulopathy (measured by ROTEM), reduced transfusion and lowered massive transfusion requirements in comparison to FFP. Disappointingly, only after a post-hoc adjustment for injury severity and brain injury was a reduction in the clinical outcome of multi-organ failure demonstrated. Perhaps had the trial not been curtailed a more meaningful clinical outcome may have been demonstrated.

The RETIC trial did show that point-of-care testing using thromboelastometry was achievable, at least with research staff support and in a time frame that allowed earlier interventions than traditional laboratory tests. Although the use of prothrombin time and activated partial thromboplastin times are recommended, results may not be available for up to 90 minutes, which may significantly delay treatment.<sup>7</sup> Furthermore, these tests monitor a limited phase of coagulation, representing only 4% of thrombin production.<sup>14</sup> In contrast, viscoelastic tests allow an overview of the entire coagulation process. Variables of clot firmness assessed by viscoelastic testing have been shown to be good predictors for the need for massive transfusion. In addition, viscoelastic tests may allow detection of coagulopathy and the need for massive transfusion when

conventional coagulation screens remain normal.<sup>15,16</sup> However, evidence for the accuracy of viscoelastic tests is limited, the agreement with standard laboratory tests has been questioned and the best parameter or parameters to target in coagulopathy is not categorically known.<sup>7,17</sup> A notable result in the RETIC trial was the persistent prolongation of the INR and APTT, particularly in the coagulation factor group, after correction of ROTEM measures and apparent clinical control of haemorrhage. The use of thromboelastometry could be seen as a limitation as viscoelastic tests are not universally available, thus limiting the generalizability of the results. Perhaps the real limitation is the continued use of traditional laboratory tests, which poorly reflect clot formation, and for which use in acute traumatic haemostasis management also lacks evidence for a survival benefit.<sup>7</sup>

Thromboelastometry clearly allowed early diagnosis of coagulopathy, which is potentially beneficial in terms of earlier intervention. Unfortunately, in the RETIC trial FFP transfusion was delayed by 40 minutes in comparison to the CFC administration. With this in mind, the coagulation factor concentrate achieved quicker reversal of the coagulopathy and bleeding (22.5 min; 95% CI, 13.5 to 40.0 vs. 128.0 min; 95% CI, 48.3 to 186.3; estimated difference -97 min; 95% CI, -126 to -60;  $P < 0.0001$ ).

A further signal of the importance of fibrinogen was that no patient in the RETIC trial died of exsanguination, in comparison to 12% in the PROPPR trial.<sup>18</sup> This is despite a higher median injury severity score in the RETIC trial (34 vs. 26), although patients in the PROPPR trial had more physiological and metabolic derangements.

The overall mortality in the RETIC trial was also surprisingly low (7%) despite high injury severity scores, with death either due to brain injury or sepsis. This perhaps highlights the limitation of an anatomically based scoring system in trauma. Although these patients had high ISS, the level of physiological derangement seemed less severe. Trauma-induced coagulopathy is associated not only with the degree of tissue injury but also the specific type of injury and presence of shock.<sup>6</sup> More specifically, as the base deficit increases the risk of coagulopathy and transfusion requirements increases.<sup>7</sup> The patients recruited were not particularly tachycardic, the majority had a systolic blood pressure above 90 mm Hg, and the base deficit and lactates were only mildly deranged, perhaps suggesting that these patients were not as systemically unwell as the ISS would suggest. Almost 60% did meet criteria for multi-organ failure. However, this was defined as a SOFA score of 3 in two organ systems - a sedated patient on noradrenaline would meet this criteria. As almost half of patients had a brain injury, perhaps an alternative definition, or removal of the CNS component might have been more appropriate. The degree of coagulopathy should also be looked at more closely. On presentation the median values of the traditional laboratory tests were within recommended range,

fibrinogen levels were above treatment levels and platelets were normal.<sup>7</sup> The FIB-10 values were also above 7mm which was identified as the level associated with major bleeding in the DIA-TRE-TIC study.<sup>20</sup> Overall, red blood cell transfusion requirements were around 5 units, and requirements for massive transfusion were relatively low.

Although the results of the RETIC study, in terms of the effectiveness of coagulation concentrates to correct coagulopathy, are clear, perhaps a larger study, or a study with a more coagulopathic cohort of patients, would have definitively shown a clinical benefit that might have changed practice decisively. Ultimately, RETIC was a single centre trial, terminated after the first interim analysis and which only demonstrated a difference in the primary outcome measure after adjustment for ISS.

### **Where this sits in the body of evidence**

The PROPPR trial evaluated the safety and effectiveness of transfusing plasma, platelets and red blood cells in a 1:1:1 ratio, compared to a 1:1:2 ratio, in 680 severely injured trauma patients (ISS 26).<sup>18</sup> There was good separation in use of blood products between the two groups. There was no difference in 24-hour mortality; 12.7% in 1:1:1 group compared to 17.0% in 1:1:2 group (difference, -4.2%; 95% CI, -9.6% to 1.1%; P = 0.12). There was also no difference in 30-day mortality; 22.4% compared to 26.1% in the 1:1:1 and 1:1:2 groups, respectively (difference, -3.7%; 95% CI, -10.2% to 2.7%; P = 0.26). In the first 24 hours, patients were less likely to die from exsanguination in the 1:1:1 group (9.2%) than the 1:1:2 group (14.6%) (difference, -5.4%; 95% CI, -10.4% to -0.5%; P = 0.03). More patients in the 1:1:1 group achieved haemostasis (86.1%) than in the 1:1:2 group (78.1%) (P = 0.006). There was no difference in time to achieve haemostasis. There was also no difference in transfusion-related complications or thromboembolic events.

The PROMMTT study was a prospective, observational study examining the effects of transfusion ratios in trauma.<sup>19</sup> In a study of 1,245 trauma patients, higher plasma : RBC and platelet : RBC ratios were associated with improved survival at 6 hours, but not at 24 hours or 30 days. The PROMMTT trial demonstrated the longer patients survived the more likely they were to have plasma : RBC and platelet : RBC ratios in excess of 1:2. By eight hours, 84% of patients had a plasma : RBC ratio of greater than 1:2, and 80% had a platelet:RBC ratio of greater than 1:2.

In a retrospective analysis of 131 trauma patients who received more than 5 units of packed red cells, with coagulation management guided by thromboelastometry, fibrinogen concentrate was administered if FIBTEM was < 10mm, while PCC was given for prolonged EXTEM results. 128 patients received fibrinogen concentrate, 98 additionally received PCC. Only 12 patients required FFP while 29 required platelets.

Mortality was significantly lower than TRISS mortality predicted (24.4% versus 33.7% (p=0.032)).<sup>21</sup>

In a further retrospective analysis, 80 patients managed by thromboelastometry with fibrinogen concentrates and/or PCC were compared with 601 patients managed with solely FFP from the Trauma Register DGU. The FFP group (ISS 35.5 ± 10.5) received a median of 6 units of FFP while the fibrinogen-PCC group (ISS 35.2 ± 12.5) received medians of 6 g of fibrinogen concentrate and 1200 U of PCC. RBC transfusion was avoided in 29% of the fibrinogen group compared to 3% in the FFP group (P< 0.001). Platelets were required in 9% of the fibrinogen group, compared with 44% of the FFP group (P< 0.001). There was no mortality difference.<sup>22</sup>

Finally in a prospective cohort study of 144 patients after blunt trauma (ISS>15), 63 patients managed with fibrinogen concentrate and/or PCC were compared with 78 patients who additionally received FFP. Patients treated with coagulation concentrates received significantly fewer units of red blood cells (RBC) and platelets than did those also receiving FFP [(RBC 2(0, 4) U vs. 9 (5, 12) U; platelets 0 (0, 0) U vs. 1 (0, 2) U, p<0.001)]. In addition, fewer patients in the coagulation concentrate group developed multiorgan failure (MOF) (18.2% vs. 37.2%, p=0.01) or sepsis (16.9% vs. 35.9%, p=0.014).<sup>23</sup>

### **Should we implement this into our practice?**

Use of fibrinogen concentrates should be considered, however, more evidence is required as to who benefits and what dose should be used.

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# Sepsis Trials



## Time to Treatment

**Seymour CW, Gesten F, Prescott H, Friedrich M, Iwashyna T, Phillips G et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. *New Engl J Med* 2017;376:2235-44**

### Introduction

Sepsis is a global public healthcare concern. In the USA, sepsis affects up to 1.5 million people annually and accounts for tens of billions of dollars in healthcare-associated spending.<sup>1,2</sup>

In a retrospective study, Kumar notably demonstrated a linear relationship between time delay to administration of antibiotics and mortality among patients in septic shock, with a 7.6% increase per untreated hour of septic shock for the first 6 hours.<sup>3</sup> The surviving sepsis campaign has incorporated this evidence into their guidelines alongside other aspects of sepsis management such as acquisition of blood cultures and measurement of serum lactate.<sup>4</sup> Different individual components of sepsis management have been grouped together in sepsis “bundles of care”, with some evidence demonstrating delivery of these sepsis bundles in an appropriate time frame may help improve mortality.<sup>5</sup>

Administration of antibiotics within one hour of recognition of sepsis has become a key goal in our management strategy for this devastating syndrome. In some states in the US, legislation has been introduced mandating the use of protocols to help drive quality improvement in the recognition and early treatment of sepsis.<sup>6</sup> The use of time-based metrics as a measure of quality of care has proven controversial, as the evidence for the relationship between early antibiotic use and survival is based on epidemiological studies using retrospective analysis of large databases and multivariate logistic regression to correct for confounding factors. Prospective studies have failed to demonstrate any meaningful difference in outcome.<sup>7</sup>

Recent evidence from well conducted randomised controlled trials suggests protocolised care offers no mortality benefit over standard care.<sup>8-10</sup> Few would argue against the overall improvement in sepsis related quality of care which has ensued following publication on Rivers’ landmark paper.<sup>11</sup> The effect of externally mandated protocols of care on mortality and other clinical outcomes is uncertain. Could the threat of financial or other penalty influence healthcare providers decisions on the floor? Are clinicians more likely to diagnose sepsis and administer antibiotics in this context? This study by Seymour examines the relationship between time to treatment and mortality in a healthcare environment influenced by mandated emergency sepsis protocols.

## Synopsis

This association study was based on the analysis of data which had been entered onto a New York State Department of Health sepsis database from April 2014 to June 2016. During this period, all emergency departments in the state were required by law to implement protocols for the early identification and treatment of sepsis. Three- and 6-hour bundles (Table 15) were mandatory components of the protocols, which could otherwise be tailored by individual hospitals.

3 Hour Sepsis Bundle	6 Hour Sepsis Bundle
Blood cultures	Re-measurement of lactate
Measurement of serum lactate	30 ml/kg fluid bolus if hypotensive or lactate > 4 mmol/l
Administration of broad spectrum antibiotics within 1 hour of diagnosis	Vasopressors for refractory hypotension (SBP < 90 mm Hg)

**Table 15. Three & six hour sepsis bundles**

Electronic case report forms were submitted on all patients who had a sepsis protocol initiated. In addition to the timing of protocol initiation and delivery of the 3- and 6- hour bundles, demographic data, co-morbidities, severity of illness scores and outcomes were mandatory components of the database. This database then served as a resource which facilitated benchmarking between hospitals and aided quality improvement within hospitals.

Regulatory authorities required broad adoption of these protocols across the state and permitted hospitals to adopt a flexible and varied approach to how they identified sepsis. Clinical and laboratory measurements could be used to screen for sepsis according to Sepsis 2 criteria.

The investigators hypothesised earlier completion of the 3-hour bundle would be associated with a reduction of in-hospital mortality. Potential confounding variables between time to treatment and outcome were identified *a priori* and multivariate logistic regression used to develop a risk adjustment model for in-hospital mortality, which was the primary outcome measure. Pre-specified sub-group analyses and separate evaluation of individual components of the sepsis bundles were completed in order to assess the effect of each on in-hospital mortality.

Patients over the age of 17, deemed to be suffering from community-acquired severe sepsis or septic shock, in whom the sepsis protocol was initiated within 6 hours of arrival

in the emergency department, were included in this study. Patients for whom the sepsis protocol was initiated more than 6 hours after admission to the emergency department were excluded. 4.6% (n = 5,126) of patients in whom the 3-hour bundle was not completed within 12 hours of protocol initiation were also excluded. 29.2% of patients screened were excluded due to the sepsis protocol being initiated prior to admission to the emergency department. Thirty-six hospitals with fewer than 50 cases of sepsis were also excluded.

49,331 patients from 149 hospitals were eligible for inclusion. Two thirds of the study population were white, with a median age of 73. 48% of patients were female. 67% had been admitted from home. 40.2% were suffering from a respiratory source of sepsis and 29.5% had confirmed positive blood cultures. 72% of patients screened positive for sepsis on clinical criteria alone, 12% screened positive based on clinical and laboratory criteria, and 16% were identified via clinical assessment from a rapid response or “code sepsis” team. 45.3% of patients were classified as suffering from septic shock.

82.5% of patients had the 3-hour bundle completed within 3 hours of initiation of the sepsis protocol. The median time to completion was 1.3 hours (IQR; 0.65 to 2.35 hours). A delay of up to 12 hours in completion of the 3-hour bundle was associated with a higher in-hospital mortality (OR for death, 1.04 per hour; 95% CI, 1.02 to 1.05; P < 0.001). Median time to administration of antibiotics was 0.95 hours (IQR, 0.35 to 1.95 hours). Delay in the administration of antibiotics was associated with a similar mortality effect (OR of death, 1.04 per hour; 95% CI 1.03 to 1.06; P < 0.001). Time to measurement of serum lactate (OR, 1.04 per hour; 95% CI, 1.02 to 1.06; P < 0.001) and acquisition of blood cultures (OR, 1.04 per hour; 95% CI, 1.02 to 1.06; P < 0.001) were associated with a similar mortality effects and probably serve as surrogates for time to antibiotic administration.

In-hospital mortality rate was 22.6% for those that completed the 3-hour bundle within three hours vs. 23.6% for those who did not complete the 3-hour bundle within three hours (P = 0.05). Time to completion of the fluid bolus was not associated with in-hospital mortality (OR of death, 1.01 per hour; 95% CI, 0.99 to 1.02; P = 0.21). Smaller, non-teaching hospitals tended to complete the bundle in a shorter time frame.

## **Critique**

This well conducted, retrospective analysis of a large (n = 49,331) sepsis database provides evidence suggesting that earlier measurement of lactate, acquisition of blood cultures, and administration of antibiotics, is associated with a reduction of in-hospital mortality. As an epidemiological study, multivariate logistic regression was used to correct for a number of confounding variables. This was not a randomised controlled

trial, thus causation cannot be deduced and the results should be seen as hypothesis generating only.

The focus of the study was time to completion of the 3-hour bundle and time to administration of first dose of antibiotics. No information is given on the adequacy of dosing of antibiotics or appropriateness of antibiotic selection. 26.8% (n = 13,233) of patients were admitted from a skilled nursing facility but we do not know the underlying rates of antibiotic resistance in these facilities, nor are we told whether patients had received prior antibiotic therapy in the community setting. No information is given on the adequacy or speed of resuscitation. Source control, which is not discussed in the paper, is also an important component of initial management of sepsis and can impact negatively on mortality if delayed, even if initial antibiotic selection is appropriate.

45% (n = 22,336) of patients in this study population were classified as having septic shock. The median lactate level was 2.7 (IQR 1.7 to 4.4). The investigators were careful to recruit only patients with a greater severity of illness, therefore the results of this study should not be generalised to other less severely ill patient populations. Furthermore, the odds ratio for hourly increase in mortality with delay are small and the difference of in-hospital mortality rate between those who completed the 3-hour bundle within three hours and those that did not was minimal (22.6% vs. 23.6%, P=0.05). Despite this, when applied to large populations, a small benefit can have a huge effect resulting in thousands of lives saved. Importantly also, there was no signal of harm with this drive to earlier therapy.

The challenge of identifying sepsis is that it remains a syndrome for which no biomarker exists. The definition of sepsis used (Sepsis 2) lacks specificity. It is possible the database contained a number of false positives; however, a manual audit of 7,492 database charts confirmed agreement with a diagnosis of severe sepsis or septic shock in 98% of cases, which strengthens the results of the study.

Time-zero in this study was taken as the time of initiation of the sepsis protocol. Of course, in reality, time-zero is an artificial creation designed to aid governance of sepsis management within emergency departments. The true time-zero is unknown and will have been hours, or indeed days, prior to the patient's emergency department admission. It has been argued, therefore, that a linear relationship between time delay and in-hospital mortality is a function of statistical methodology and lacks biological plausibility.<sup>7</sup>

Legislation demanding protocolisation of early sepsis care in New York State emergency departments was introduced in 2013.<sup>6</sup> It is possible hospital emergency departments

may feel under duress to identify and treat sepsis rapidly. At best this may lead to erroneous coding, at worst it may subject non-infected patients to the potential side-effects and risks of widespread antibiotic prescription, as well as increasing the risk of antimicrobial resistance.

The Rivers trial in 2001 demonstrated an in-hospital mortality rate of 30.5% in the early goal directed therapy group, compared to 46.5% in the standard treatment group.<sup>11</sup> The in-hospital mortality rate of 22.8% in this study may reflect the trend for improvement in overall recognition and management of sepsis (rather than protocolisation) that ensued following the Rivers trial. The 3- and 6- hour bundles may have contributed to this improvement in care.

The in-hospital mortality rate observed compares favourably with the mortality rates observed in the ProMISe, ProCESS and ARISE trials, which have now clearly demonstrated protocolisation offers no mortality benefit over standard care.<sup>8-10</sup> Whilst the need for early administration of broad spectrum antibiotics in cases of sepsis is widely accepted, given the current lack of evidence for protocolised management in early sepsis care, the continued statutory requirement for this demanded by the State of New York and others in America must be questioned. It would seem prudent to separate protocolised early antibiotic therapy, in cases of sepsis, from protocolised fluid and haemodynamic targeted therapy.

As our knowledge of sepsis pathophysiology continues to expand, the results of this study provide limited evidence of the association between early completion of a 3 hour sepsis bundle and a small mortality benefit. The only way to determine if earlier antibiotic administration really improves mortality is via proper randomised controlled trials. This is unlikely to occur anytime soon based on ethical grounds.

### **Where this sits in the body of evidence**

Kumar et al carried out a retrospective analysis of 3 separate cohorts of patients suffering from septic shock. Medical records of 2,731 patients diagnosed with septic shock were examined. 558 patients who received antibiotic prior to the onset of hypotension were excluded from the primary analysis. Multivariate logistic regression was used to investigate the temporal relationship between onset of hypotension, delay to first antibiotic administration and in-hospital mortality. Hypotension was defined as a mean arterial pressure < 65 mm Hg, systolic BP < 90 mm Hg or a drop in systolic pressure of > 40 mm Hg systolic from baseline. During the first 6 hours after the onset of recurrent or persistent hypotension, each hour of delay in antibiotic administration was associated with a mean decrease in survival of 7.6% (range 3.3 to 9.9%).<sup>3</sup>

In a retrospective study of 35,000 patients suffering from sepsis, severe sepsis and septic shock, Liu and colleagues used multivariate logistic regression analysis to estimate the adjusted odds of in-hospital mortality based on timing of antibiotic administration. Patients admitted to the emergency department, receiving antibiotics within 6 hours of registration and subsequently admitted to hospital were included. Time of emergency department registration was used as time-zero. Median time to antibiotic administration was 2.1 hours (IQR 1.4 to 3.1 hours). The odds ratio for in-hospital mortality for each hour of delay in administration of antibiotics was 1.09 (95% CI, 1.05 to 1.13). The odds were greatest for those suffering from septic shock (OR, 1.8; 95% CI, 0.8% to 3.0%; P = 0.001).<sup>12</sup>

In a UK multi-centre, prospective, observational cohort study, key determinants of mortality were assessed in 679 patients suffering from gram negative bacteraemia. Empiric antibiotics were deemed to be appropriate if blood cultures on the day of administration subsequently demonstrated sensitivity *in vitro* to the antibiotic given. Mortality was adjusted for patient demographics, co-morbidities and illness severity. All-cause mortality was 8% at 7 days and 15% at 30 days. Empiric antibiotics were deemed to be inappropriate in 34% of cases. Inappropriate antibiotic therapy was not, however, associated with mortality at either time point (adjusted OR, 0.82; 95% CI, 0.35 to 1.94). Older age, increase in co-morbidities, inflammatory response and severity of illness at presentation were found to be the main determinants of mortality.<sup>13</sup>

In a prospective, multi-centre, observational study in 44 German ICUs compliance with an infection management guideline was assessed. 1,011 patients suffering severe sepsis or septic shock were included. The primary outcome measure was 28 day mortality. 36.6% (n = 370) of patients received antibiotic therapy within 1 hour of recognition of organ dysfunction. Median time to antibiotic therapy was 2.1 hours (IQR 0.8 to 6.0) and to source control was 3 hours (IQR -0.1 to 13.7). No linear relationship was found between antibiotic therapy and mortality. Patients who received source control later than 6 hours after onset of organ dysfunction had a significantly higher 28-day mortality (42.9 vs. 26.7%; P < 0.001).<sup>14</sup>

A Dutch prospective, observational study involving three emergency departments examined time to antibiotic administration and the impact on hospital length of stay and 28-day mortality. 1,168 consecutive patients, over the age of 17, with suspected infection, treated with iv antibiotics, and admitted as in-patients were included. Confounding variables such as appropriateness of antibiotics and haemodynamic resuscitation were accounted for. Illness severity was stratified as mild, moderate and severe as per the PIRO classification (predisposition, infection, response and organ failure). The primary outcome measure was the number of days surviving outside



hospital by day 28. There was no association between time to antibiotic administration and survival at this time-point. 28-day mortality rate was 10% and, although this was a secondary outcome measure, no association with time to antibiotic administration was found.<sup>15</sup>

In a retrospective analysis of prospectively collected data, Ryoo et al. examined the time to antibiotic administration and outcome, in the context of protocol driven resuscitation, among 426 patients suffering from septic shock. Guidance on empirical antibiotic prescription, based on likely source of infection, was used to try and minimise inappropriate antibiotic prescriptions. The median time from shock recognition to antibiotic administration was 91.5 minutes (IQR 47 to 158 min). The primary outcome measure was 28-day mortality. No association between mortality and hourly delay in antibiotic administration, up to 5 hours after shock recognition, was elucidated.<sup>16</sup>

Timing of antibiotic administration both from emergency department triage and from recognition of severe sepsis/septic shock were analysed in a meta-analysis which included 11 cohort studies. No statistical difference in mortality was detected between those that received antibiotics within 3 hours of triage and those that did not (OR, 1.16; 95% CI, 0.92 to 1.46; P = 0.21). Similarly, for those who received antibiotics within 1 hour of recognition of severe sepsis or septic shock, no difference in mortality was detected (OR, 1.46; 95% CI, 0.89 to 2.4; P = 0.13). The investigators caution against the use of a time metric to antibiotic administration as a marker of quality of sepsis care.<sup>17</sup>

### **Should we use protocolised, time-driven, mandated sepsis care?**

Early antibiotic therapy should be administered in sepsis and septic shock, however, current evidence strongly suggests mandated fluid and haemodynamic management is not beneficial over usual care.

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## SSSP-2

**Andrews B, Semler M, Muchemwa L, Kelly P, Lakhi S, Heimbürger D et al. Effect of an Early Resuscitation Protocol on In-hospital Mortality Among Adults With Sepsis and Hypotension – A Randomized Clinical Trial. JAMA 2017; 318(13): 1233-1240**

Sepsis has become almost a defining syndrome for critical care, being the leading cause of the speciality-specific condition of multiple-organ failure.<sup>1</sup> Accordingly, ICU clinicians and researchers are at the forefront of efforts to define the disease process, evaluate ways to mitigate its effects and disseminate knowledge to others in the hope that early recognition and treatment may improve outcomes. Despite a paucity of evidence for specific therapies or protocolised resuscitation bundles, current consensus would hold that early recognition, simple initial treatments and access to organ-support for those deteriorating are vital components of a healthcare system's response to sepsis.

It is also true, however, that the majority of deaths due to infection occur in less developed economies who lack the above infrastructure.<sup>2</sup> It is reasonable to posit that if this (including intensive care) was available worldwide then improvements in sepsis mortality similar to, or exceeding, that seen in risk-adjusted Western populations in recent years may be achievable.<sup>1</sup> However, it is important to consider that the infecting organisms and baseline health status and physiology of those affected may be markedly different to that studied in European, Australasian or American populations. The study of sepsis interventions in-situ in places such as sub-Saharan Africa is therefore of great importance. The FEAST study by Maitland et al. was a towering achievement in this regard, demonstrating that the core sepsis intervention of fluid boluses was associated with immediate clinical improvement but caused increased mortality in septic African children.<sup>3</sup> This has helped to 'square the circle' by challenging assumptions regarding the benefit of fluid therapy in Western populations and influencing research direction here. The Simplified Severe Sepsis Protocol 2 (SSSP-2) study aimed to build on that legacy.

### **Synopsis**

SSSP-2 was a single-centre non-blinded parallel group randomised controlled trial conducted in a Zambian referral hospital, testing protocolised sepsis management against usual care. Eligible adults met the Sepsis-2 criteria for septic shock (suspected infection with  $\geq 2$  systemic inflammatory response syndrome (SIRS) criteria with hypotension {systolic blood pressure (SBP)  $\leq 90$  mm Hg or mean arterial pressure (MAP)  $\leq 65$  mm Hg}). Screening of patients {on presentation to the emergency department (ED)} occurred on weekdays from October 2012 to November 2013. Those who needed surgery or with gastrointestinal bleeding (without fever), severe renal disease or signs of

congestive cardiac failure were excluded. Also excluded were patients with severe hypoxaemia (arterial oxygen saturation (SpO<sub>2</sub>) < 90% with respiratory rate (RR) > 40 breaths/min; based on their response in a previous similar trial by the same authors.<sup>4</sup> Informed consent was obtained from the patient or their legal representative, followed by selection of an envelope containing the computer-generated random group allocation.

The intervention (SSSP) group received the haemodynamic management protocol for 6 hours (Table 16). Observations were recorded hourly and fluid administration stopped if jugular venous pressure (JVP) was above sternal angle, SpO<sub>2</sub> decreased by 3% or RR increased by five breaths/min. In the usual care (UC) group therapies were at clinician discretion. All patients were allocated a study nurse and had routine and study-specific blood tests sent. Fluid volumes administered were recorded and patients followed up until 28 days (or death). Patients, clinicians and study nurses were all aware of the group allocation; personnel assessing outcomes and analysing data were blinded.

Intervention	Protocol requirement
IV fluids	2 litres in first hour. 2 further litres in next 4 hours unless JVP* raised.
Blood culture and malaria blood smear	Within 1 hour
Antibiotics	After culture, within 1 hour, chosen by physician
Dopamine	Titrate to MAP > 65 mm Hg if required after fluid bolus.
Blood transfusion	(if available), for haemoglobin < 70 g/L or severe pallor.

**Table 16: Simplified severe sepsis protocol used in intervention group**

\*JVP= Jugular venous pressure.

The primary outcome was in-hospital mortality. A sample size of 212 patients was calculated to have 80% power ( $\alpha=0.05$ ) to detect an absolute mortality reduction of 20% from the predicted control group mortality of 65% (derived from the investigators' previously published study). Pre-specified secondary outcomes included mortality at 28 days, process outcomes including protocol adherence, and safety outcomes including worsening oxygenation. Planned analysis was by modified intention-to-treat; excluding those who were identified as ineligible after randomisation but before intervention.

Over the study period 382 of 3,515 screened patients met inclusion criteria. 170 were excluded (83 for hypoxaemia, 27 for congestive cardiac failure / raised JVP, 30 refused consent, 30 other reasons) and 212 were randomised, three were incorrectly included and subsequently excluded, leaving 106 and 103 patients assessed for the primary

outcome in the SSSP and UC groups respectively. A further 16 patients (9 SSSP, 6 UC) were lost to follow up after hospital discharge leaving 28-day mortality data incomplete.

There were no reported baseline differences between groups. Overall, mean (SD) age was 47 (12.4) years, 89.5% were human immunodeficiency virus (HIV) positive, 45% had a history of Mycobacterium tuberculosis (TB) infection. Most patients were malnourished as assessed by upper arm circumference. 64% were unable to ambulate, this was for a median (IQR) of 16.5 (10 - 35) and 10 (7 - 21) days in the SSSP / UC groups respectively.

Median (IQR) values did not differ for SBP {83 (77 - 87) vs. 83 (75 - 87) mm Hg}; heart rate {115 (104 - 129) vs. 115 (103 - 130) /min}; or RR {30 (28-38) vs. 32 (28 - 39)} breaths/min in the SSSP / UC groups respectively. Median (IQR) Simplified Acute Physiology Score-3 (SAPS-3) was 55 (50 - 65) vs. 57 (50 - 66) also in the SSSP / UC groups respectively. Mean (SD) haemoglobin (Hb) concentration in both groups was 78 (3.0) g/L; median (IQR) serum albumin concentration was 21 (17 - 26) / 23 (19 - 28) g/L in the SSSSP / UC groups. Median (IQR) serum lactate overall was 4.3 (2.8 - 7.7) mmol/L. At admission the following were recorded as the source of sepsis (each patient could have more than one diagnosis): malaria (11%), pneumonia (49%), TB (63%), gastrointestinal (23%) and central nervous system (CNS) (14%).

By six hours the SSSP group had received more fluid than UC patients (median 3.5 L vs. 2.0 L; mean difference, 1.2 L (95% CI, 1.0 to 1.5 L);  $P < 0.001$ ); and dopamine more frequently (14% vs. 2% of patients,  $P = 0.001$ ). Blood transfusion rates did not differ (16% vs. 13%;  $P = 0.48$ ). By this stage 39% of the SSSP group had received  $\geq 4$ L of fluid, the fluid protocol had been stopped for respiratory distress (30%), raised JVP (9%) or other reasons in the others. In the UC group 52% received no fluid bolus, overall a variety of regimens were used comprising zero to four litres "fast" followed by up to four litres over 24 hours. The SSSP group still had significantly more fluid administered at 24 hours but not at 72 hours {median (IQR) 5.0 (3.5 - 6.5) vs. 4.0 (3.0 - 6.0);  $P = 0.33$ }. Median (IQR) time to antibiotics did not differ {2.0 (0.7 - 4.1) hours vs. 1.5 (0.5 - 2.8) hours;  $P = 0.15$ }.

There were no significant differences in systolic or diastolic blood pressures at two or six hours {median (IQR) SBP at six hours 95 (90 - 104) mmHg (SSSP) vs. 96 (90 - 105) mm Hg (UC);  $P = 0.95$ . Fall in serum lactate was slightly greater with the intervention {change -1.2 (-3.4 to 0.3) mmol/L (SSSP) vs. -0.5 (-2.2 to 1.1) mmol/L (UC);  $P = 0.02$ }. More SSSP patients had a respiratory deterioration during the first six hours (RR rose by  $\geq 5$  breaths/min or SpO<sub>2</sub> fell by  $\geq 3\%$ ): 36% vs. 23%;  $P = 0.03$ ; but not persisting beyond this (17% vs. 15%;  $P = 0.63$ ).

Mortality was significantly increased in the SSSP group, both in-hospital (primary outcome): 48% vs. 33%; difference, 15% (95% CI, 2% to 28%); RR, 1.46 (95% CI, 1.04 to 2.05);  $P = 0.03$ ); and at 28 days (data for 194 patients): 67% vs. 45%; difference 22% (95% CI, 8% to 35%); RR 1.48 (95% CI, 1.14 to 1.91);  $P = 0.002$ . This difference held when adjusted for enrolment SAPS-3, and remained consistent across the pre-specified subgroups (baseline coma score / Hb / SAPS-3 / serum lactate / JVP / HIV status). Kaplan-Meier survival curves separated within two days. Median (IQR) length of hospital stay was 5 (3 - 8) vs 7 (4 - 12) days in the SSSP / UC groups ( $P = 0.01$ ). There were two diagnosed cases of iatrogenic pulmonary oedema in the SSSP group, only one patient was admitted to the intensive care unit.

## Critique

This important and well-conducted study demonstrates clearly the crucial role of well conducted in-situ research in preventing potentially widespread harm from importing aggressive (if well-intentioned) interventions from resource-intensive into resource-limited settings. Confidence in the conclusion that the SSSP increased in-hospital mortality is increased by the completeness of follow-up and consistency of results within pre-specified subgroups.

Before considering its place in the literature there are a few potential caveats to mention. The SSSP directed fluids by volume rather than based on patient weight, in the absence of facilities to weigh non-ambulant patients ideal body weight could have been estimated by measuring (recumbent) patient height. Noradrenaline rather than dopamine is the preferred vasopressor in the West, but its peripheral use is controversial. The control-group fluid administration was highly variable and in some cases approached that suggested by the SSSP, lessening between-group differences. Oxygen saturations were a key safety measure but not reported separately in the manuscript or supplementary material; nor was the MAP which was the target for vasopressor dosing. Jugular venous pressure measurement may be an imprecise way of monitoring for circulatory overload.

This was a single-centre unblinded study of limited size, with the observed control-group mortality approximately half that predicted, and analysed by modified intention-to-treat. The fragility index is two - if this many extra patients in the control group had died then the statistical significance of the mortality difference would have been lost.<sup>5</sup> It is therefore possible that a larger, multicentre study with a similar protocol may find no increased mortality with the intervention (in an analogous but opposite manner to that seen with protocolised resuscitation in resource-intensive settings as discussed below).

The rationale for SSSP-2 rested largely on attempting to replicate the survival benefit seen with large-volume fluid resuscitation in Rivers' 2001 study of early goal-directed therapy (EGDT) in 263 septic emergency department patients, wherein the intervention group received a median of nearly five litres of fluid within six hours, compared to 3.5 litres in the control group.<sup>6</sup> The investigators comment in the study protocol that in sub-Saharan Africa "insufficient amounts of IV fluids are administered to septic patients ... in Uganda Jacob et al. found that only 35% of patients with sepsis and hypotension received one or more litres of fluid in the first six hours".

The recruitment period ran from 2012-13 at a time when the results of the FEAST and SSSP-1 studies were known. The rationale for SSSP-2 held that the harmful effects of fluid boluses seen in FEAST may be paediatric-specific; and took steps to not recruit those with respiratory distress who seemed to be at-risk in SSSP-1. At the same time the three multi-national studies which re-examined protocolised EGDT resuscitation in European, US and Australasian populations were also recruiting. With the ProCESS, ARISE and ProMISE studies all ultimately reporting no survival benefit<sup>7</sup> current knowledge would suggest that protocolised resuscitation is equivalent to (modern) standard therapy in Western healthcare systems but likely to be harmful in Sub-Saharan African settings.

The investigators and accompanying editorial discuss reasons for this. The patients often presented in this study with un-resuscitated but long-established illness, with two thirds unable to ambulate for a number of weeks. There was an extremely high incidence of tuberculosis, HIV infection (half of which was untreated), anaemia and malnutrition with hypo-albuminaemia. Hypotension may have been chronic and adaptive rather than acute and pathological. It is entirely plausible that these characteristics would predispose to pulmonary oedema with or without cardiac failure with aggressive salt and volume loading. This itself may be more likely to be fatal in the setting of almost zero access to mechanical ventilation for this population.

It should be acknowledged finally that almost all studies in this area allowed or encouraged liberal (if less) early fluid administration in the control group. The FEAST study remains a powerful reminder that this has not been shown definitively to be safe or effective. The CLASSIC trial showed it is possible to restrict fluids effectively in the post-resuscitation phase,<sup>8</sup> we should welcome cautious efforts to test attempting this earlier in the course of the septic process.

### **Where this sits in the body of the evidence**

Maitland et al performed a stratified (severe hypotension or not), multi-centre, randomized control trial in a resource-limited setting in sub-Saharan Africa, comparing a



fluid bolus (20 to 40 ml/kg 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.<sup>3</sup> 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 intracranial pressure and neurological sequela in the three groups ( $P = 0.92$ ).

Andrews et al in 2014 published the results of SSSP-1, in which the same protocol as used in SSSP-2 was used.<sup>4</sup> 112 of the planned 342 patients were enrolled, patients in the intervention group received more fluids by six hours (2.8 litres vs 1.6 litres,  $p < 0.001$ ), with few receiving dopamine and no difference in blood transfusion rates. In-hospital mortality was not significantly different between groups (64% SSSP vs 61% control), but the trial was stopped early due to concern about the 100% mortality (8/8 patients) seen in those in the SSSP group with hypoxaemic respiratory distress at baseline.

Rivers and colleagues randomly assigned 263 patients with severe sepsis or septic shock to six hours of early goal-directed therapy, guided by ScvO<sub>2</sub> monitoring, or standard care in the emergency department prior to ICU admission.<sup>6</sup> 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,  $P < 0.001$ ), 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 US ProCESS trial was the first of three contemporary studies examining early goal-directed therapy in septic shock.<sup>9</sup> 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;  $P < 0.001$ ), vasopressors, inotropes and red cell transfusions. 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.<sup>10</sup> 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-centred outcomes.

The third modern EGDT was the UK ProMiSe trial in 1,260 patients with early septic shock.<sup>11</sup> As before, the EGDT group (n = 630) received more interventions, including total fluids (median/IQR: EGDT group 2,000 ml (1,150 to 3,000) vs 1784 ml (1075 to 2775), within the first 6 hours. Although there was no difference in the primary outcome of 90 day mortality (EGDT group 29.5% vs. usual care 29.2%; RR1.01, 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 ( $6.4 \pm 3.8$  vs.  $5.6 \pm 3.8$ ), proportion requiring advanced circulatory support (37% vs 30.9%) and median (IQR) length of ICU stay (2.6 (1.0 to 5.8) vs 2.2 (0.0 to 5.3 days). The probability that EGDT was cost-effective was less than 20%.

The Fluids and Catheters Treatment Trials (FACTT) compared a conservative with liberal fluid strategy in 1,000 patients with acute lung injury.<sup>12</sup> Haemodynamic management was achieved with a complex protocol. At day 7, the conservative group achieved a net neutral fluid balance ( $-136 \pm 491$  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 ( $14.6 \pm 0.5$  vs.  $12.1 \pm 0.5$ ; P < 0.001).

The CLASSIC Scandinavian multicentre randomised parallel-group feasibility trial by Hjortrup et al included 151 adults with septic shock admitted to ICU following initial fluid resuscitation.<sup>8</sup> Those randomised to the intervention received further fluid boluses only with signs of hypoperfusion (lactate  $\geq 4$  mmol/l, MAP  $\leq 50$  mmHg despite noradrenaline, severe mottling or early oliguria); those in the control group were allowed boluses at clinician discretion. Fluid volumes were lower in the intervention group by 1.2 L (95 % CI, -2.0 to -0.4; P < 0.001) at day 5 despite protocol violations in 27/75 patients. Clinical outcomes tended to favour the restrictive group, a follow-up study powered for these outcomes is planned.

### **Should we implement this resuscitation into our practice?**

No. Aggressive early resuscitation in this health-care setting seems to be harmful and should be avoided. Its use in resource-intensive settings may yet be further refined.

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## **HYPERS2S**

**Asfar P, Schortgen F, Boisramé-Helms J, Charpentier J, Guérot E, Megarbane B et al. Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial. *Lancet Respir Med* 2017;5(3):180-190**

The original Surviving Sepsis Campaign promoted the widespread algorithmic use of large volume fluid resuscitation and increased FiO<sub>2</sub> to enhance oxygen delivery in septic patients, following the improved survival seen with this approach in the study by Rivers et al in 2001.<sup>1</sup> This was in keeping with the theory that cellular hypoxia caused by inadequate oxygen delivery was central to sepsis pathophysiology. The mortality of critically ill patients with severe sepsis has since significantly improved; however, three large, multi-centre, international trials failed to replicate the Rivers' study success and attention has refocused on individual resuscitation therapy components.<sup>2</sup>

Conversely, there is now evidence that excessive fluid therapy is associated with worse outcomes.<sup>3</sup> Hypertonic saline may allow low volume fluid resuscitation and limit this complication, although evidence for this is limited.<sup>4</sup> High tissue oxygen tensions have a moderate effect on increasing blood oxygen content, but may additionally aid haemodynamics in shock by vasoconstriction and have been shown to reduce the incidence of surgical site infections consistent with a bactericidal effect. However, there is concern about worse outcomes seen with higher PaO<sub>2</sub>s in diverse large ICU population studies.<sup>5</sup> The HYPERS2S trial used a two-by-two factorial design to simultaneously study both hypertonic saline and hyperoxia as interventions of interest in the same population of patients with septic shock:

### **Synopsis**

HYPERS2S was conducted in 22 French ICUs between 2012 and 2014. Eligible adults were mechanically ventilated and had severe sepsis (two or more systemic inflammatory response syndrome (SIRS) criteria, proven or suspected infection, one or more organ dysfunction) which was early and fluid refractory (absence of response to 20 ml/kg of crystalloid or colloid and  $\geq 0.1$   $\mu\text{g}/\text{kg}/\text{min}$  of noradrenaline or adrenaline infusion for  $\leq 6$  hours). Those with intracranial hypertension, cardiac failure, dysnatraemia ( $< 130$  or  $> 145$  mmol/L), post cardiac arrest, treatment limitation, unlikely survival, pregnancy or severe hypoxaemia (PaO<sub>2</sub>:FiO<sub>2</sub>  $\leq 100$  mm Hg with PEEP  $\geq 5$  cm H<sub>2</sub>O) were excluded. As patients with acute respiratory distress syndrome (ARDS) may be at particular risk from fluid overload or extremes of oxygenation, patients were stratified at inclusion by its presence or absence.

There were four study groups (hyperoxia or normoxia; each with hypertonic or isotonic saline) with computerised block randomisation in a 1:1:1:1 ratio; stratified by site and presence / absence of ARDS ( $\text{PaO}_2:\text{FiO}_2 \leq 200$  mm Hg and bilateral chest radiograph infiltrates). Hyperoxia ( $\text{FiO}_2$  1.0) or normoxia (target arterial haemoglobin oxygen saturation ( $\text{SaO}_2$ ) 88% - 95%) were delivered for 24 hours. The fluid administration algorithm ran over 72 hours and required 280 ml boluses of 0.9% or 3.0% sodium chloride over 10 minutes if criteria were met (Table 17); this could be repeated up to 4 times if these criteria remained. Further boluses required efforts to exclude cor pulmonale and document a low cardiac index or  $\text{ScvO}_2$  alongside low filling pressures, or a dynamic assessment of fluid responsiveness. Boluses were stopped if oxygenation deteriorated ( $\text{SpO}_2 < 88\%$  or  $\text{PaO}_2 < 55$  mmHg) and the protocol stopped for hypernatraemia ( $\text{Na}^+ > 155$  mmol/L or  $> 12$  mmol/L rise in 24hrs), open label 0.9% saline was then used. Patients, staff and researchers were blinded to the study fluid allocation, the oxygenation strategy was open-label. Lung-protective ventilation and a PEEP-titration strategy were recommended.

800 patients were required to have an 80% power, with a two sided alpha of 0.05, to detect a 10% difference in the primary outcome of all-cause 28-day mortality, in hyperoxia and hypertonic saline vs. normoxia and isotonic saline. Baseline mortality was predicted to be 45%. A range of pre-specified secondary and safety endpoints were assessed. Interaction between the two treatments was not expected.

Criteria for Fluid Bolus	
Overt fluid losses	Mottling or capillary refill time > 2 sec
Tachycardia HR > 120/min	Low cardiac output or filling pressure
SBP < 90 or MAP < 65 mmHg or MAP ↓ 20%	Increasing vasopressor dose
Serum lactate > 2 mmol/l	$\text{ScvO}_2 < 70\%^{\#}$
Urine output < 0.5 ml/kg/hr	

**Table 17. Criteria for fluid bolus**

*SBP = systolic blood pressure; MAP = mean arterial blood pressure  $\text{ScvO}_2$  = central venous oxyhaemoglobin saturation*

1,555 of 2,466 screened patients met the inclusion criteria; 808 met exclusion criteria (most often severe hypoxaemia, treatment limitation, expected demise and dysnatraemia); and 305 were excluded for technical reasons. The remaining 442 patients were randomised, with 8 excluded from analysis (five withdrew consent, three were under guardianship). All initially received the correct allocated treatment, but 16/219 patients allocated to hyperoxia did not receive a  $\text{FiO}_2$  of 1.0 for the full 24 hours; and

there were protocol violations in 27/224 assigned to isotonic saline and 29/218 assigned to hypertonic saline. Baseline characteristics were mostly well matched between groups, a typical patient being a 68 year old male without major comorbidity and with an initial Sequential Organ Failure Assessment (SOFA) score of 10; 30% were postoperative. The source of infection was lung or abdomen in  $\approx 70\%$  and community acquired in  $\approx 62\%$ . Median values show that most patients had a moderate tachycardia, lactic acidosis and adequate MAP on a median dose of  $0.4 \mu\text{g}/\text{kg}/\text{min}$  of noradrenaline. 51% of patients met the set criteria for ARDS, 53% had a  $\text{PaO}_2 > 120 \text{ mm Hg}$  on study entry. Patients assigned to hypertonic saline had a higher lactate and incidence of cirrhosis ( $P < 0.05$ ).

Separation between the groups was achieved in the oxygenation arm of the study. Patients assigned to hyperoxia had a higher median  $\text{PO}_2$  (277 vs. 93 mm Hg,  $P < 0.001$ ) and  $\text{SaO}_2$  at 24 hours (99% vs. 97%,  $P < 0.0001$ ); with no difference at 72 hours. Separation was less impressive in the fluid arm; at 72 hours the hypertonic saline group showed a significant reduction in mean (SD) volume of study fluid infused ( $1.4 \text{ L} \pm 1.0$  vs.  $2.5 \text{ L} \pm 2.3$ ,  $P < 0.0001$ ) but no difference in overall mean fluid intake ( $7.6 \text{ L} \pm 5.1$  vs.  $7.6 \text{ L} \pm 4.1$ ,  $P = 0.49$ ). This was caused by a higher rate of open-label fluid administered in the hypertonic saline group after study fluid administration was stopped in 84 patients with hypernatraemia.

Recruitment was halted for futility at the recommendation of the Data and Safety Monitoring Board (DSMB) after the second planned interim safety analysis. Whilst there was no significant difference in the primary endpoint with either intervention, mortality was numerically higher with both: hyperoxia vs. normoxia (28-day mortality 43% vs. 35%;  $P = 0.12$ ); hypertonic saline vs. isotonic saline (28-day mortality 42% vs. 37%;  $P = 0.25$ ). Analysis of the primary endpoint showed no evidence of clinical interaction between the two interventions nor influence of the presence or absence of ARDS, and these factors were not included in further analyses (in a change from the originally published statistical plan).

Amongst a total of 38 secondary outcomes, there was no difference in 90-day mortality or ICU length of stay with either intervention. Statistical significance was only seen in one of 16 reported SOFA score time-points (favouring hyperoxia at day 7) and mean ventilation-free days (favouring normoxia). Hyperoxia was associated with a higher rate of adverse events than normoxia, both overall (rate 85% vs. 76%;  $P = 0.02$ ) and for atelectasis (12% vs. 6%;  $P = 0.04$ ) and possibly ICU-acquired weakness (not significant, 11% vs. 6%;  $P = 0.06$ ). There were no significant differences in adverse event rates between hypertonic and isotonic saline, apart from a small increase in chest radiograph scores at 24 hrs.

## Critique

This study is a significant addition to the critical care literature. It was well run, it investigated areas of current interest, the population was well described and of appropriate acuity, with a mortality within the range expected. The interventions were well applied and follow-up was near complete. With the caveat of the early cessation of the trial, this encourages confidence in the conclusion that hyperoxia and hypertonic saline showed no demonstrable benefit in critically ill patients with septic shock. It is worth, however, examining these results alongside consideration of aspects of the trial methodology.

The factorial design allowed the simultaneous use of the entire trial population to examine both hyperoxia and hypertonic saline, in contrast to a parallel group trial which would require individual power calculations for each intervention and (in this case) double the number of required patients. However, its success is dependent on there being no interaction between the interventions:<sup>6</sup> this was the investigators' *a priori* assumption, but one could also postulate the deleterious effects of hyperoxia on the lung in ARDS may be impacted by the degree of excess lung tissue fluid. It is noted in the study that mortality was numerically lowest in patients exposed to neither intervention. No statistical evidence of interaction was found, but exclusion of a clinically relevant interaction would ordinarily require a larger sample size than the trial itself, which was not achieved in HYPERS2S, particularly with the early trial cessation effectively halving recruitment, making the investigators' assessment of the clinical likelihood of an interaction crucial.

Early trial termination for futility has been criticised as it may miss a true effect signal, especially as conditional power calculations depend on extrapolating current event rates which may be invalid.<sup>7</sup> In this case the DSMB understandably recommended cessation; the (numerically) higher mortality with both interventions at interim analysis means, if continuing to full recruitment, the trial would have been very unlikely to yield a positive effect, yet expose further patients to potential harm. There is, however, no definite statistical evidence of harm: the excess of adverse event rates in the hyperoxia group was largely driven by an increase in atelectasis which may not translate to adverse patient outcomes, and with over 50 secondary or adverse event outcomes reported, without correction for multiple comparisons, there is a significant risk of type 1 error. The reported increase in ICU-acquired weakness and decrease in liver-SOFA score seen with hyperoxia should be interpreted with caution. The smaller trial numbers mean the published study had less ability to identify important secondary effects (or a significant mortality difference); predefined criteria for stopping for futility may avoid this being a source of future criticism.

The lack of benefit seen with hypertonic saline may be explained by several reasons. There was frequent unblinding of treatment allocation, as the chosen administration algorithm was unsuccessful. The 39% incidence of severe hypernatraemia necessitated switching to unblinded isotonic saline, but this also contributing to the lack of difference in overall fluid volumes. Even the moderate increase in serum sodium seen in most patients may be deleterious; hypernatraemia is independently associated with increased ICU mortality and the permitted rise in serum sodium of 12 mmol/24hr is double that recommended when treating non-emergency hyponatraemia.<sup>8,9</sup> There was also significant hyperchloraemia, which may be deleterious (especially if in future compared to a balanced crystalloid). The excess of cirrhosis and hyperlactaemia in the hypertonic saline group may have unbalanced the baseline risk. The fluid algorithm was quite aggressive leading to significant positive fluid balance. Three multicentre trials of similar aggressive resuscitation algorithms have failed to show benefit.<sup>2</sup> Resuscitation was ongoing before entry into the trial; thus, hypertonic saline may have shown more benefit as an initial fluid bolus.

There was, however, no major signal of harm and future trials could investigate its use in distinct circumstances, such as the initial fluid in a truly restrictive fluid algorithm. The study also describes the entry criteria as “septic shock”, where in fact the patients met the 2001 consensus criteria for “severe sepsis”, as well as incorrectly describing the preparation of the 0.9% saline study fluid.

It is possible the increased mortality with hyperoxia could have reached statistical significance if the trial had continued to full recruitment. A paper proposing the potential benefits of hyperoxia (which shares authors with the study) is included in the supplementary material as rationale for the trial.<sup>10</sup> It elucidates the potential benefits based on mainly animal studies (vasoconstriction with catecholamine-sparing effect, possible anti-inflammatory and anti-microbial effects), and suggests the known deleterious effects (including reactive oxygen species and pulmonary toxicity) may have been overstated in the early phase of septic shock, especially if a protective ventilation strategy is used.

Although full ethical approval was obtained for this study, it should be stated that severe hyperoxia has long been avoided in ARDS studies, and that large scale retrospective studies had identified hyperoxia as an independent risk factor for mortality in specific ICU populations<sup>5</sup>. Additional oxygen was detrimental in a randomised trial in non-critically ill patients with myocardial infarction and of no benefit in stroke.<sup>11,12</sup> One prospective single centre study has recently reported a decreased mortality with a restrictive oxygenation strategy<sup>13</sup>; a multi-centre trial is ongoing (ICU-



ROX, CTG 1415-04). Hyperoxia is unphysiological with known harmful effects, is linked to poor outcomes and this study shows no evidence of benefit alongside possible harm.

### **Where this sits in the body of evidence**

In 2014 Damiani and colleagues performed a systematic review of largely retrospective multi-centre cohort studies, evaluating arterial hyperoxia in the critically ill.<sup>5</sup> Hyperoxia was associated with increased mortality in 3 specific populations: post cardiac arrest (n = 19,144; OR, 1.42; 95% CI, 1.04 to 1.92; P = 0.028); post stroke (n=5537; OR, 1.23; 95% CI, 1.06 to 1.43; P = 0.005); and post traumatic brain injury (n = 7,488; OR, 1.41; 95% CI, 1.03 to 1.94; P = 0.032). The four studies which examined hyperoxia in generic mechanically ventilated populations (n = 18,9143) were excessively heterogenous in design and outcome to give a pooled estimate of risk; individual estimates of odds ratios for mortality ranged from 0.73 to 2.86. Randomised controlled trials of oxygenation targets were recommended.

The Oxygen-ICU investigators randomised 480 ICU patients to conservative (PaO<sub>2</sub> 70 - 100 mm Hg, SpO<sub>2</sub> 94 - 98%) or conventional (PaO<sub>2</sub> ≤ 150 mm Hg or SpO<sub>2</sub> ≥ 97%) oxygen therapy in a single Italian ICU; 434 patients were included in a modified intention-to-treat analysis.<sup>13</sup> 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.

In 2016 the Australian and New Zealand Intensive Care Society Clinical Trials Group reported a pilot study where 103 mechanically ventilated patients were randomised to a target SpO<sub>2</sub> of 88 - 92% or ≥ 96%.<sup>14</sup> Separation between groups was achieved (primary outcome), with no significant differences in clinical outcomes. True hyperoxia was uncommon, with a PaO<sub>2</sub> > 120 mm Hg seen in only 13% of measurements in the liberal oxygenation arm. A large-scale trial of oxygenation targets by the same group is underway (ICU-ROX, CTG 1415-04).

In 2012 Meyhoff et al. reported on the mortality of patients 16 months after cessation of the PROXI trial, which randomised 1,386 patients undergoing laparotomy to a perioperative FiO<sub>2</sub> of 0.8 or 0.3.<sup>15</sup> Those randomised to hyperoxia had a significantly greater long-term mortality (23.2% vs. 18.3%; HR, 1.3; 95% CI, 1.03 to 1.64; P = 0.003. This relationship held for the subgroup of the 51% of patients undergoing cancer surgery.

In 2011 van Haren et al reported a pilot study in which 24 invasively monitored adults with septic shock were randomised to a bolus of 6% hydroxylethyl starch suspended in either 250 ml of 7.2% NaCl or 500 ml of 0.9% NaCl.<sup>16</sup> There was no difference in the

primary outcome of gastric tonometry values; although there were positive effects of hypertonic saline on cardiac contractility and vasopressor requirement, felt to be independent of plasma volume expansion. No patient outcome data was collected.

Oliveira randomised 29 mechanically ventilated patients with sepsis and stable haemodynamics to a 250 ml bolus of 0.9% saline or a hypertonic 7.5% NaCl / 8% dextran solution.<sup>17</sup> There was a significantly higher initial volume effect with the hypertonic solution, with an increased cardiac index, stroke volume and pulmonary artery occlusion pressure. No differences were seen at 180 minutes.

In contrast, Fang compared 3 solutions, 3.5% NaCl, 0.9% NaCl and 5% Sodium bicarbonate, as a 5 ml/kg initial fluid bolus in 94 adults with de-novo sepsis and hypotension.<sup>18</sup> Patients already requiring inotropes, vasopressors or mechanical ventilation were excluded. There were no differences seen between the groups in the degree of improvement in MAP, heart rate or echocardiography-assessed cardiac output.

### **Should we implement this into our practice?**

No – Hyperoxia has shown no benefit and may well be harmful. Hypertonic saline, as used, didn't reduce overall fluid volumes and was predictably limited by hypernatraemia.

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## S-TAFE

**Rouze A, Loridant S, Poissy J, Dervaux B, Sendid B, Cornu M et al. Biomarker-based strategy for early discontinuation of empirical antifungal treatment in critically ill patients: a randomised controlled trial. *Intensive Care Med* 2017;43:1668-1677**

### Introduction

Candidaemia is amongst the most common of ICU-acquired bloodstream infections. In addition to increasing morbidity and length of stay for patients, invasive *candida* infection is associated with a mortality rate of up to 50%.<sup>1,2</sup> Critically ill patients are at higher risk of candidaemia because of immunosuppression, plus other risk factors such as central venous catheters, steroid use and antibiotic exposure.<sup>2</sup>

The mainstay of identification of candidaemia is currently through isolation of fungal species from blood cultures, the results of which are often delayed. Time delay to commencement of antifungal treatment in patients with candidaemia is associated with increased mortality.<sup>3</sup> For these reasons many antifungals are prescribed on an empirical basis for patients who are deemed to have risk factors for invasive *candida* infection and exhibit signs of infection. It is thought up to two-thirds of patients receiving systemic antifungals in ICU have been prescribed them on an empirical basis.<sup>4</sup> With guidelines recommending a duration of treatment of two weeks for patients who have improved with antifungals but without evidence of invasive *candida* infection, the current strategy results in significant costs, exposure and risks the emergence of resistant *candida* strains.<sup>1,5</sup>

Recent guidelines recommend the use of serological biomarkers to exclude the diagnosis of invasive *candida* infection, thus allowing earlier discontinuation of empirical antifungal treatment.<sup>1,5</sup> The evidence-base for this strategy comes from two observational studies.<sup>6,7</sup> No previous randomised controlled trial has assessed this approach. 1,3- $\beta$ -D-glucan, mannan, anti-mannan antibody, *Candida albicans* germ tube antibody (CAGTA) have all been assessed and varying sensitivities, specificities, positive and negative predictive values, have resulted, depending on the patient population analysed, the *candida* species referred to, the threshold level of biomarker used, and whether the biomarkers have been used in isolation or in combination.<sup>8</sup>

### Synopsis

S-TAFE was a single centre, non-blinded, randomised controlled trial, conducted at a 50 bedded, university affiliated, mixed medical-surgical ICU in Lille, France. The investigators hypothesised a strategy of measuring a biomarker panel at day 0 and day 4

would reduce the duration of empirical antifungal treatment for patients in whom these agents had been prescribed.

The unit guideline for empirical antifungal prescription stipulated patients had to be suffering a persistent fever, for greater than 48 hours, despite antibiotics and exhibit signs of haemodynamic instability in the last 12 hours, and also had to fulfil at least one major and two minor criteria, as outlined below (Table 18). No data on physician compliance with this guideline is presented in either the text or supplementary material.

Major Criteria	Minor Criteria
Systemic antibiotic therapy	Total parenteral nutrition
Central venous catheter	Dialysis
	Major surgery
	Pancreatitis
	Use of corticosteroids

**Table 18. Ostrosky-Zeichner risk prediction model**

Adult patients in whom empirical antifungal therapy had been commenced by the clinical team due to the suspicion of candidaemia, and who were expected to remain in ICU for 6 or more days, were eligible for inclusion. Patients with neutropenia, immunosuppression of any cause, solid organ transplantation, those with documented invasive candidiasis or who had been treated with an antifungal in the preceding 3 months, were excluded, as were patients who had received any type of chemotherapy in the preceding 3 months.

Patients were randomised in a 1:1 ratio to the biomarker strategy group or usual care group (control group) using a computer-based random-number generator and sealed, opaque numbered envelopes opened by a study investigator.

The biomarker strategy group (intervention group) had serum levels of (1,3)- $\beta$ -D-glucan, mannan and anti-mannan antibody measured on day 0 and day 4. An algorithm based on cut-off levels of each biomarker was constructed. This algorithm resulted in a recommendation to either continue with, or discontinue, the empirical antifungal treatment which had been started. The control group had empirical antifungal treatment continued for 14 days after initiation, in those who showed clinical improvement or in whom invasive candidiasis was proven. No biomarkers were measured in the control group.

The primary clinical team determined the choice of empirical antifungal agent based on local guidelines. All patients had 3 sets of blood cultures performed prior to

commencing an antifungal and had 5 body sites sampled once a week to determine colonisation rates. If invasive *candida* infection was confirmed in either group then 14 days of antifungal treatment was given.

The primary outcome measure was the proportion of patients (excluding those who died) in whom antifungal therapy was stopped early i.e. less than 7 days, after the initiation of empirical antifungal treatment. Secondary outcome measures included total duration of antifungal therapy, proportion of patients subsequently colonised with *candida* and percentage of patients with subsequently proven or probable invasive candidiasis.

For the power calculation, it was estimated 3% of the control group would have early discontinuation of empirical antifungal treatment and the biomarker strategy would increase this proportion to 30%. To identify this effect, 45 patients were needed in each group to achieve 90% power at a two-sided alpha level of 5%. Allowing for mortality, 55 patients in each group were required.

During the study period, of 2,908 patients admitted to the ICU, 18% (n = 510) were treated with an antifungal agent and assessed for eligibility for the trial. 400 patients were excluded after screening. The principal reasons for exclusion were that the antifungal used was not empirical (n = 123) and that the expected length of ICU stay was < 6 days (n = 63). 110 patients were randomised, 1 patient withdrew consent, leaving 54 patients in the intervention group and 55 patients in the control group.

The groups did not differ significantly at ICU admission. 63% of recruited patients were male with a median age of 64 (IQR 56 to 72) vs. 59 (IQR 7 to 69) in the intervention vs. control groups, respectively (P = 0.104). 72% (n = 79) of patients in this study were admitted medically with 29% (n = 32) having received a recent course of antibiotics. Duration of ICU stay prior to randomisation was a median of 5 days (IQR 2 to 12) vs. 8 days (IQR 3 to 13) in the intervention and control groups, respectively, with 94% (n = 102) of patients mechanically ventilated and 98% (n = 107) having a central venous catheter in-situ at randomisation. Parenteral nutrition and steroids were prescribed for 38% (n = 41) and 45% (n = 49) of patients, respectively.

72% (n = 79) of patients had evidence of fungal colonisation at randomisation and 3% (n = 3) had evidence of candidaemia. The empirical antifungal agent of choice was fluconazole, used in 50% patients (n = 54), followed by caspofungin, which was prescribed empirically for 41% of patients (n = 45).

Early discontinuation of empirical antifungal treatment was implemented in 54% (n = 29) of patients in the intervention group vs. 2% (n = 1) of patients in the control group (OR 62.6; 95% CI, 8.1 to 486, P < 0.0001). The duration of antifungal treatment was significantly shorter in the intervention vs. control group also, 6 days (IQR 4 to 13) vs. 13 days (IQR 12 to 14), respectively (P < 0.0001). There were no significant differences in any of the secondary outcomes, including subsequent proven or probable invasive candidiasis, ICU length of stay, ICU and 28-day mortality, or total expenditure.

## Critique

This is the first randomised controlled trial assessing the impact of fungal biomarkers on the discontinuation of antifungal agents in critically ill adults. As such, this is an important and interesting study. However, it was a small, single centred, non-blinded study, which will require the same hypothesis to be tested in a much larger, multi-centre, randomised controlled trial to clarify the role biomarkers may play in discontinuing empirical antifungal treatment.

This was a low risk ICU population for invasive candidiasis, as the trial excluded many key risk factors, such as neutropaenia, any form of immunosuppression, solid organ transplantation and chemotherapy within the last three months. Most patients were admitted medically rather than surgically, but the rate of parenteral nutrition, 38%, is surprisingly high for a predominantly medical patient cohort. Similarly 45% of patients were treated with corticosteroids which seems high. This is in contrast with the recently published EMPIRICUS study, a multi-centre randomised controlled trial of empirical micafungin in which only 9% of patients were receiving steroids.<sup>9</sup>

S-TAFE appears to have recruited a relatively sick patient group, with almost all recruited patients receiving mechanical ventilation and 32% receiving renal replacement therapy (RRT). At randomisation, median SOFA score was 9 (IQR 5 to 12) vs. 7 (5 to 11) in the intervention and control groups, respectively.

In order for empirical antifungals to be prescribed, a clinical suspicion of invasive candidiasis, defined as a persistent fever (> 48 hours) and/or haemodynamic instability (> 12 hours) despite well-conducted antibiotic therapy had to be present. In addition, the patient had to fulfil the Ostrosky-Zeichner criteria outlined above. It is unclear how haemodynamic instability was defined, what proportion of patients were on vasopressor/inotropic support at randomisation or how much fluid patients had received. The term "well-conducted antibiotic therapy" is also non-specific. Physician compliance with this unit guideline is also unknown.

The ICU mortality rates of 33% (n = 18) and 29% (n = 16) in the intervention and control groups, respectively, seem high, although the length of ICU stay was also long in both groups, 26 (IQR16 to 32) vs. 25 (IQR14 to 33) days.

The use of empirical antifungals in this ICU was relatively high during the study period, with 13% of patients receiving an antifungal. As the study was unblinded this may have introduced bias, with clinicians perhaps more inclined to think of, and prescribe, an antifungal for their patients during the study period. The criteria used for commencement of an antifungal was also quite liberally defined, as discussed above.

The combination of serum biomarkers also warrants discussion. The algorithm used in this study has not been previously validated but was constructed by the investigators because the institution involved had previous experience in measuring and acting on these biomarkers. The algorithm used may not be replicable in other countries and more high risk ICU populations. There are eleven possible pathways within the algorithm which patients may follow resulting in a recommendation to either continue or cease antifungal therapy, but a breakdown of how many patients followed which pathway is not given. Given the complexity of the pathway it is difficult to envisage how it would be applied in clinical practice.

The sensitivity and specificity for each biomarker varies for differing *candida* species. The background prevalence of *albicans* versus *non-albicans* fungal infection in this ICU is not given, but with 41% (n = 45) of patients receiving empirical caspofungin as a first line antifungal in this study it raises the question as to whether there is a significant *non-albicans* issue in this particular ICU. The secondary outcomes may give a clue as to why some physicians opted for caspofungin rather than fluconazole initially; 8% (n = 9) of patients in this study subsequently grew a resistant *Candida*.

The investigators discuss the sensitivity and negative predictive value of (1,3)- $\beta$ -D-glucan. However a test should also have a high specificity and positive predictive value. The investigators allude to the moderate positive predictive value of the biomarker panel used which may have led to the unnecessary continuation of antifungal treatment in some of these low risk patients.

If a patient in this study had a positive mannan antigen test at day 0 or day 4, the antifungal was continued for 14 days. It is unclear how many patients this actually applied to. In effect, the biomarker algorithm used may have been a combination of anti-mannan and (1,3)- $\beta$ -D-glucan. The threshold serum level of each biomarker used to define positivity is also important. The sensitivity and negative predictive value of (1,3)- $\beta$ -D-glucan changes as the threshold serum level changes. This study used a threshold



level of 80 pg/ml. Anti-mannan was considered positive at > 20 UA/ml. This is higher than the manufacturer's recommendation of 10 UA/ml in order to try to increase its sensitivity and negative predictive value. The combination of (1,3)- $\beta$ -D-glucan at a threshold of 80 pg/ml and anti-mannan antibody in a previous study of ICU patients with severe abdominal conditions had a sensitivity of 74%, specificity of 50%, positive predictive value of 18.5% and negative predictive value of 92.7%.<sup>10</sup> Thus, a high rate of false positive results is possible with this combination; 46% (n = 25) of the intervention group did not have the antifungal discontinued based on biomarker results.

Although more patients in the biomarker group had antifungal therapy discontinued, the 95% confidence interval for the odds ratio was extremely wide (OR 62.6, 95% CI, 8.1 to 486) indicating a significant amount of uncertainty regarding the true influence of a biomarker strategy in antifungal discontinuation. For example, other factors can result in raised levels of 1,3- $\beta$ -D-glucan such as haemodialysis, albumin administration, transfusion of blood products and bacterial sepsis.<sup>8</sup> Nearly a third (n = 35) of patients in this trial were receiving RRT but we are not told of the transfusion of blood products in this patient group.

At present the optimal combination of biomarkers is not known. Other biomarkers strategies, such as the *Candida albicans* germ tube antibody CAGTA and PCR-based *candida* detection methods, may be more accurate in detecting invasive candidiasis than the method employed in this study, but this will require further study with much larger numbers of patients.

### **Where this sits in the body of evidence**

The EMPIRICUS study was a multi-centre, double-blind, randomised controlled trial of empirical micafungin vs. placebo in critically ill patients with suspected invasive candidiasis.<sup>9</sup> 260 patients were randomised in 19 centres across France. There was no difference in the primary endpoint (28-day survival free of proven invasive fungal infection) between groups, 68% vs. 60.2% in the micafungin vs. placebo group, respectively (HR, 1.35; 95% CI, 0.87 to 2.08; P = 0.18). Interestingly 1,3- $\beta$ -D-glucan levels were elevated in both groups, with levels being unaffected by micafungin therapy. When outcomes were analysed for those patients with elevated 1,3- $\beta$ -D-glucan levels, no difference was found, suggesting this biomarker was not a useful guide to therapy in this patient population.

A meta-analysis of studies examining the diagnostic utility of 1,3- $\beta$ -D-glucan for invasive fungal infections included 16 studies, 10 of which utilised a cohort design and 6 a case-control design. Eleven of the studies were of patients diagnosed with a haematological disorder. 2,979 patients were included. The pooled sensitivity of 1,3- $\beta$ -D-glucan was

76.8% (95% CI, 67.1% to 84.3%) and specificity 85.3% (95% CI, 79.6% to 89.7%). There was a significant amount of statistical heterogeneity in the included studies. The investigators concluded 1,3- $\beta$ -D-glucan was useful in distinguishing invasive fungal infection from no fungal infection but cautioned clarification regarding the timing and frequency of testing, and what constitutes a positive test result. In addition, the influence of concurrent bacteraemia on diagnostic performance needs to be considered.<sup>11</sup>

In a retrospective, case-control study 1,3- $\beta$ -D-glucan, mannan antibody, anti-mannan antigen and the Cand-Tec *Candida* antigen were analysed independently, and in combination, to evaluate the use of these biomarkers for the diagnosis of invasive candidaemia. All patients admitted to a German university affiliated ICU over an eleven year period were considered for inclusion. Only those patients identified with positive blood cultures for candidaemia, and who had an archived sample from day 0 to day 2, were recruited (n = 56). One hundred culture negative patients and 100 patients with confirmed bacteraemia acted as controls. The optimal combination of biomarkers used appeared to be 1,3- $\beta$ -D-glucan and mannan antigen, with a sensitivity of 89.3% and specificity of 85%. The combination of anti-mannan antibody and mannan antigen had an unacceptably low specificity of 63%. The Cand-Tec antigen had a sensitivity of just 13%.<sup>12</sup>

In a prospective, multi-centre, observational cohort study of 176 non-neutropenic patients admitted to the ICU with a severe abdominal conditions, 1,3- $\beta$ -D-glucan, CAGTA, CRP and procacitonin were assessed for their ability to discriminate between invasive candidiasis and *candida* colonisation. Patients were recruited from 18 tertiary level Spanish ICUs. 76% of patients were surgical admissions. Surveillance cultures, together with measurement of the above biomarkers, were performed on the third day of ICU stay and twice-weekly for 4 weeks. In patients who were colonised with *candida*, a statistical model was constructed to predict the risk of invasive candidiasis. 1,3- $\beta$ -D-glucan levels of > 259 pg/mL, combined with CAGTA-positive results, were accurately able to discriminate colonisation from invasive candidiasis. In this study, patients with this combination had almost a 60% chance of invasive candidiasis. Using a cut-off of 259 pg/mL, 1,3- $\beta$ -D-glucan was highly specific but had a low sensitivity (51.6%).<sup>10</sup>

### **Should we routinely use a biomarker-based strategy for managing empirical antifungal therapy?**

Not at present. Although S-TAFE reported a significant difference in favour of the biomarker-based group, this small, single centre study requires replication in a larger, multi-centre trial before widespread implementation.

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## INSTINCT

**Madsen MB, Hjortrup PB, Hansen MB, Lange T, Norrby-Teglund A, Hyldegaard O et al. Immunoglobulin G for patients with necrotising soft tissue infection (INSTINCT): a randomised, blinded, placebo-controlled trial. *Intensive Care Med.* 2017;43(11):1585-1593**

### Introduction

Necrotising soft tissue infection can be a devastating disease, with mortality as high as 35%.<sup>1</sup> The infection is characterized by rapid progression, with significant local tissue destruction and varying amounts of early or late systemic toxicity depending on the strain of bacteria and toxins produced. Yet diagnosis can be difficult, as skin findings can be disproportionate to the severity of symptoms and degree of systemic upset. Although scoring systems have been used, the diagnosis often depends on a high index of suspicion and confirmation during surgical exploration.<sup>2</sup> Subsequent treatment relies on early wide surgical debridement, broad-spectrum antibiotics and supportive care. A further adjunctive therapy in this septic population is the use of immunoglobulin therapy.

Immunoglobulins modulate the host immune response in multiple ways. Perhaps the obvious potential benefits in a septic exotoxin-driven disease process are the ability to neutralise bacterial exotoxin and enhancing the recognition and phagocytosis of bacteria.<sup>3</sup> Immunoglobulins also play a role in the inhibition and scavenging of inflammatory mediators, as well as displaying direct anti-inflammatory effects and causing attenuation of cellular apoptosis, effects that may be beneficial in a septic population.<sup>3</sup> A further rational for immunoglobulin therapy is the apparent deficiency in critical illness, although the prognostic significance of this is unclear.<sup>4,5</sup> With an apparent physiological rational, and a paucity of high quality evidence in the field, the INSTINCT trial is important in the understanding of immunoglobulin treatment in necrotising soft tissue infections.

### Synopsis

INSTINCT was a single centre, randomised control trial performed at a regional referral centre in Copenhagen. The primary aim was to assess the effect of intravenous immunoglobulin G (IVIG) on self-reported physical function after intensive care admission with necrotising soft tissue infection.

Adult patients with confirmed necrotising infection at surgical exploration, who were admitted, or planned to be admitted, to the intensive care were eligible for recruitment. The presence of necrotising soft tissue infection was determined during surgical

debridement. Patients were excluded if more than 48 hours had passed since diagnosis, they had received more than one dose of immunoglobulin, they had a hypersensitivity to immunoglobulin or they had hyperprolinaemia. Pregnant or breastfeeding women were also excluded.

Eligible patients were randomised using a computer-generated, sealed envelope system, with stratification depending on the presence of head, neck or extremity source. This aimed to obtain a sub-group with a higher rate of streptococcal or staphylococcal infections. Patients received either IVIG 25 g/day for three consecutive days or placebo (an equivalent volume of normal saline). The intervention was blinded to clinical staff caring for the patient and research staff. All subsequent care was at the discretion of the clinical team. The institution had protocols for management of necrotising infections, including repeated surgical interventions, standard antibiotics (meropenem, clindamycin and ciprofloxacin) and three sessions of hyperbaric oxygen therapy.

The primary outcome was patient reported physical function, as the physical component summary (PCS) score of the Medical Outcomes Study 36-item short form health survey version 2 (SF-36) at day 180 after randomisation. Secondary outcomes were mortality at 28, 90 and 180 days and time to resolution of shock (defined as a systolic above 90 mm Hg for 24 hours without support). In addition, data on bleeding and transfusion requirements, organ failure, as measured using the SOFA score for the first seven days, and the requirement for renal replacement therapy, ventilation and vasopressor support were captured. The number of days alive and off life support at 90 days, and also the days alive and out of hospital at 180 days, were recorded. Any serious adverse event, including the requirement for amputation, were also recorded.

On the basis of a mean of 42 (SD 11) on the PCS score of SF-36 at day 180 in the placebo group, a total sample size of 100 patients was calculated to give an 80% power with an alpha of 0.05 to detect a 7 point increase in the PCS score in the immunoglobulin group. The primary analysis was a regression analysis adjusted for the site of infection, performed in the intention-to-treat population. The primary outcome was also analysed with adjustment for age and SOFA score at baseline, missing PCS data, in two per protocol populations and in sub-groups with and without infection of the head/neck/extremities.

Over a 2 year period, a total of 129 patients were screened with 100 randomised, 50 to each group. The patients recruited were around 60 years of age and mainly resided at home (93%). Almost two-thirds were male with around a quarter suffering from diabetes. Virtually all patients were ventilated (95%), with 40% having septic shock. The median SOFA score (excluding the CNS score) was 8 in the IVIG group and 7 in the

placebo group. Baseline characteristics were similar, with the exception of acute kidney injury, which was more common in the IVIG group (10% versus 2%), and time from admission to surgical intervention, which was longer in the placebo group (18 hours versus 25 hours), as well as the proportion of patients who had received IVIG prior to admission, which was higher in the placebo group (16% versus 40%). The site of infection was distributed equally; 52% of patients had infection in the head/neck/extremity sites, with 48% classified as others. The infections were mainly polymicrobial (68%). In the monomicrobial patients, there was a difference in the rate of group A strep (56% IVIG group versus 31% placebo group) and also in the rates of staph. aureus (0% IVIG group versus 23% placebo group).

In terms of the intervention, the median dose administered in both groups was three. The trial protocol was discontinued in 4 IVIG patients (1 withdrawal, 3 adverse reactions) and 7 patients in the placebo (3 withdrawals, 4 adverse reactions). One placebo patient subsequently developed a further indication for IVIG and was given two doses.

In total, 62 patients had the primary outcome evaluated at 180 days. There were 25 deaths (who were assigned a score of 0). The SF-36 was not obtained in 13 patients. All patients were included in the secondary outcomes analysis. There was no difference in the primary outcome; the median PCS score in the IVIG group was 36 (IQR, 0 - 43) compared to 31 (IQR, 0 - 47) in the placebo group (mean adjusted difference 1; 95% CI, -7 to 10;  $P = 0.81$ ). Nor was there any difference in the adjusted primary outcome analysis. There were no significant differences in any secondary outcome measures.

## Critique

Prior to the INSTINCT trial, only one randomised controlled trial had investigated the efficacy of immunoglobulin treatment for necrotising soft tissue infection.<sup>6</sup> Although the impact of immunoglobulins in this study seemed positive, the trial was curtailed after only 21 patients due to enrolment difficulties. Conflicting observational data constitute the remaining evidence-base for the use of immunoglobulins in soft tissue infection,<sup>7,8</sup> with guidelines non-committal on the intervention.<sup>9</sup> INSTINCT is therefore the largest trial investigating immunoglobulins in necrotising soft tissue infection.

The trial hypothesised that IVIG would benefit patients with necrotising soft tissue infection by primarily inhibiting bacterial toxins, reducing inflammation and diminishing the area of the affected site, which would lead to faster recovery. As a measure of recovery the investigators chose the physical component of the Medical Outcomes Study 36-item short form health survey, which, although initially used in a medical population, has been validated in intensive care.<sup>10</sup> However, by combining death and the PCS together (by giving a score of 0 if a patient died), such a composite outcome can be

misleading.<sup>11</sup> In fact, the PCS scores were higher amongst survivors in the placebo group, although this was not significant. Perhaps a larger trial might have been powered to allow for separate analysis of these outcome measures.

Although a single centre study, 100 patients were recruited over a relatively short time scale of 2 years, due to the comparatively unique regional management of patients with necrotising soft tissue infections in Denmark. This centralisation ensured that once patients were transferred to the regional centre, management was standardised, and as the trial was well conducted with adequate blinding, this perhaps allows a true understanding of the effects of the intervention. However it was not possible to standardise treatment prior to transfer. Of note, there was a substantial difference in time to operation from hospital admission {median(IQR); 18 hrs (6 - 40) vs. 25 hrs (6 - 50)} in favour of the intervention group. Delayed surgical management is known to be associated with poorer outcomes.<sup>1</sup>

A further confounder was inclusion of patients who had already received immunoglobulins prior to transfer, with 40% of patients in the control arm having already received immunoglobulins prior to randomisation. The optimum dosing and timing of administration of immunoglobulins in sepsis is not known,<sup>3</sup> although just a single dose has the potential to blunt any treatment effect. This also creates a scenario where many patients in the placebo group received the treatment earlier than in the intervention group, with earlier treatment, as with other interventions in septic patients, thought to be associated with improved outcomes.<sup>12</sup>

It is the septic patient population that immunoglobulins have been more extensively investigated. A recent meta analysis suggested a mortality benefit, although when low quality trials were eliminated any beneficial effects were negated.<sup>13</sup> A criticism of many previous immunoglobulin trials were the inconsistent inclusion criteria.<sup>3</sup> In the INSTINCT trial, patients were randomised only after confirmation of diagnosis at surgery and if ICU admission was planned. This ensured that only necrotising infections were enrolled but in doing so may have delayed the administration of the intervention. Furthermore, the inclusion criteria did not include any measure of disease severity or sepsis diagnosis. Although the SAPS II indicated a mortality rate around 25%, only 40% of patients had septic shock, rates of acute kidney injury were low and the overall mortality was only 12%. The low mortality may reflect better outcomes from an experienced centre but overall perhaps a sicker patient population might have benefited more from the intervention.

Stratification by site of infection was performed to obtain a group of patients with higher rates of either streptococcal or staphylococcal infections and therefore, as per



the rationale for the trial, potentially more to gain from the intervention. However, the overall rates of group A streptococcal or staphylococcal infections were low and the occurrence of infections was unbalanced between the groups. Perhaps a larger cohort would have lessened this inequality.

Other trials have incorporated more complex methods of patient selection for immunoglobulin therapy. Sepsis is associated with a decrease in circulating immunoglobulin levels, with some studies suggesting that low levels have prognostic significance.<sup>4</sup> Although the INSTINCT trial did not measure immunoglobulin levels, a strategy for targeted treatment based on immunoglobulin concentrations and clinical trajectory has been previously suggested.<sup>3</sup> However, the largest immunoglobulin trial (SBITS) which measured immunoglobulins, showed wide variation in levels and failed to demonstrate any prognostic significance.<sup>5</sup> Similarly to plasma cortisol levels, immunoglobulin concentrations in sepsis vary considerably. A better understanding of the reasons for these variations are perhaps required before immunoglobulin levels can be considered as an indication for therapy. Also, improved understanding of immunoglobulin levels in sepsis and of the pharmacokinetics of administered immunoglobulin may better inform the optimal dose in these patients. Current dose regimens have varied considerably in both dose administered and duration of therapy.<sup>3</sup> The dose in the INSTINCT trial, 25 g daily for 3 days, was lower than many previous studies and therefore could have been sub therapeutic.<sup>3</sup> A previous meta-analysis suggested doses  $> 1$  g/kg or therapy for  $\geq 2$  days was associated with a survival benefit.<sup>14</sup>

A further consideration was the proportion of group A streptococcal or staphylococcal infections present, which may have been more amenable to the use of IVIG. However, the majority of cases were polymicrobial infections with a significant proportion of gram-negative organisms. IgM enriched preparations contain antibodies against lipopolysaccharides of *Escherichia coli*, *Pseudomonas* and *Klebsiella*, bacteria which were involved in almost half of the polymicrobial infections.<sup>15</sup> Furthermore, the promotion of phagocytosis by IgM may be superior to that of IgG.<sup>16</sup> These potential benefits could account for the reported stronger treatment effect of IgM in sepsis.<sup>11</sup> The investigators in the INSTINCT trial were unable to demonstrate a treatment effect. Given the obvious confounders and the small size of this trial, along with the gaps in current knowledge of timing, dose and target population, in retrospect, perhaps this result is not surprising.

Before further clinical trials are conducted there have been calls for additional basic research in immunoglobulin physiology and pharmacokinetics in sepsis to better inform the design of large trials.<sup>3</sup> As immunotherapy has largely failed to significantly improve outcomes in sepsis, it is arguable that perhaps our basic understanding of sepsis needs to improve before further immunotherapy trials are conducted.

## Where this sits in the body of evidence

In a multi-center, blinded, placebo-controlled trial, that was prematurely terminated because of slow recruitment, 21 patients with toxic shock syndrome were randomised to IVIG (n = 10) or placebo (n = 11).<sup>6</sup> The primary end point was 28-day mortality. Mortality was non-significantly 3.6 times higher in the placebo group. A significant decrease in organ failure score on days 2 (P = 0.02) and 3 (P = 0.04) was noted in the IVIG group. A significant increase in plasma neutralizing activity against superantigens was also seen in the IVIG group (P = 0.03).

In a randomised, double-blind, placebo-controlled, multi-center trial, using a complicated sepsis scoring system, 653 patients were assigned to either placebo (n = 303) or IVIG (n = 321).<sup>5</sup> IVIG was dosed at 0.6 g/kg on day 0 and 0.3 g/kg on day 1. The primary end point was 28-day mortality. Secondary end points were 7-day mortality, change in morbidity, and pulmonary function at day 4. The 28-day mortality rate was 37.3% in the placebo group and 39.3% in the IVIG group (P = 0.67). "No difference was seen in 7-day mortality, morbidity or 4-day pulmonary function.

In a double-blind trial, surgical patients with intra-abdominal sepsis were randomised to receive IVIG (7 mL/kg/day for 5 days) or placebo (5% albumin). Fifty-six patients were recruited.<sup>17</sup> In the intent-to-treat analysis, the mortality rate was reduced from 48.1% in the placebo group to 27.5% in the IVIG group (P = 0.06). There was no difference in organ failure, organ dysfunction or reoperation rates. Initial antibiotic was the only variable independently associated with death.

In another placebo controlled trial, 42 septic patients were randomised to intravenous Pentaglobin (38 g/l IgG, 6 g/l IgM, and 6 g/l IgA) or standard therapy.<sup>18</sup> Pentaglobin dose was 5 ml/kg/day infused over 6 hours and repeated for 3 days. Procalcitonin measurements were taken daily. Severity of illness and development of organ failure were assessed. Procalcitonin levels showed a significant decrease in the Pentaglobin group (P < 0.001); however, there was no difference in SOFA scores.

In prospective, randomised clinical trial, fifty-five patients with septic shock were allocated to either immunoglobulin preparation (n = 27) (containing high titers of antibodies specific for bacterial endotoxin) for 72 hours or standard care.<sup>19</sup> Mortality was 4% in the immunoglobulin group compared to 32% in the control group (P < 0.01).

### **Should we routinely use IVIG in the management of necrotizing soft tissue infections?**

There is no evidence to support the use of immunoglobulin therapy to improve physical outcome in necrotizing soft tissue infection. Larger trials are required.

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# Miscellaneous Trials



## ICE-CUB2

**Guidet B, Leblanc G, Simon T, Woimant M, Quenot J, Ganansia O et al. Effect of Systematic Intensive Care Unit Triage on Long-term Mortality Among Critically Ill Elderly Patients in France. JAMA 2017;318(15):1450-1459**

### Introduction

Those funding ICUs would probably expect that admission to ICU is offered to those most likely to benefit from this finite resource, and that admission not be affected by personal or institutional biases. However, large-scale cohort studies have demonstrated that survival with reasonable function following ICU discharge has become commonplace in conditions which previously may have been considered to not benefit from admission. With hindsight it is likely that large numbers of patients with conditions such as chronic obstructive pulmonary disease (COPD) and haematological malignancy were historically inappropriately denied ICU level care.<sup>1</sup> Worldwide the elderly are an ever-increasing demographic class and whilst the mean age of ICU admission in most Western countries has risen in recent decades there remains a concern that inappropriate therapeutic nihilism may remain.<sup>2</sup> The ICE-CUB1 study suggested that ICU admission for elderly patients presenting with critical illnesses to French Emergency Departments was relatively uncommon, even in the presence of objective predictors of success, and seemed to depend on chronological age and the presenting hospital.<sup>3</sup> One caveat to consider is that whilst it may seem self-evident that ICU admission is likely to benefit those with critical illness, this has been surprisingly hard to prove.<sup>4</sup> ICE-CUB2 was an attempt to shed further light on these issues.

### Synopsis

ICE-CUB2 studied an intervention to systematically promote ICU admission in all suitable elderly patients presenting with a predefined critical illness, and compared this to usual practice. The trial ran in French Emergency Departments (EDs) from 2012-2015 and was cluster-randomised – hospitals were the units of randomisation rather than individuals. Intervention hospitals were asked to introduce a multi-faceted program in which ED and ICU clinicians were required to jointly evaluate eligible patients at the bedside and arrange ICU admission, unless they decided this was unwarranted. This was backed up by site visits, pamphlets, posters, a newsletter and monthly meetings wherein ED and ICU jointly reviewed included patients. ICU admission decisions in control (standard practice) hospitals were made as normal. There was no ED screening log in either group, with no data recorded on those meeting inclusion criteria but not enrolled. Randomisation of hospitals was stratified by geographical area, presence of a geriatrics unit and by the median annual number of ED visits.

Eligible patients were  $\geq 75$  years without active cancer and with preserved functional status (assessed by Index of Independence in Activities of Daily Living (ADL) Score  $\geq 4$ ) and no cachexia; these being predictors of survival in the ICE-CUB1 study. The ADL score ranges from 0 (totally dependent) to 6 (fully independent). Those who were in ED for  $> 24$  hours or refused to participate were excluded. The need for individual patient consent was waived under French law but participants were informed orally when able to understand and free to withdraw assent to data use. Thirty-one predefined clinical presentations were used, as previously described by the investigators, being adapted by translation into French and Delphi method consensus from the 1999 Society of Critical Care Medicine (SCCM) (US) guidelines.<sup>5</sup> They generally comprised conditions likely to require organ support, excluding those felt not to be appropriate for the elderly target population, such as anoxic coma and intra-cerebral haemorrhage. As an example the cardiac group included cardiogenic shock, congestive heart failure requiring non-invasive ventilation (NIV) and arrhythmia.

The primary outcome was 6-month mortality; secondary outcomes included ICU admission rate, hospital mortality and 6-month assessment of functional status, quality of life (QOL) and caregiver burden. The planned recruitment of 3,000 patients was estimated to have 74% power to detect a 6% mortality difference between groups (2-sided  $\alpha = 0.05$ ), assuming a predicted 32% control group mortality; adjusted for cluster-randomisation. Analyses were pre-specified and by intention-to-treat; excepting a post-hoc exploratory analysis of the characteristics of ICU-admitted patients. In all 3,037 patients were enrolled, with 1,519 patients in the 11 intervention hospitals and 1,518 in the 13 standard practice hospitals (this occurred at a slower than expected rate, necessitating an extension of the recruitment period). The number of patients screened for inclusion was estimated as 2.7% of the annual ED visits of  $>75$  year-olds, based on ICE-CUB1 data (8% related to critical conditions, 33% of which fulfilled inclusion criteria). One patient withdrew consent, all others were included in the primary analysis.

Baseline characteristics were generally similar between groups. Median (IQR) age was 85 (81-89), 55% were female. The commonest qualifying presentations were septic shock (413/3,036 patients, 13.6%), requirement for NIV for respiratory failure (11.4%) or cardiac failure (7.2%), and pneumonia (8.2%). 10.5% had coma (various causes), 2% had surgical diagnoses and 3% required immediate mechanical ventilation for respiratory failure. These, as well as usual living situation and co-existing conditions, were balanced between groups, apart from a higher incidence of heart failure in the intervention group (15 vs. 11%). This group also had a worse illness severity score {median Simplified Acute Physiology Score III (SAPS-III) at enrolment 64 vs. 59;  $P < 0.001$ }. The systematic strategy resulted in measurable changes in behaviour in the intervention group. ICU physicians were involved more in the triage process (97% vs. 62%;  $P < 0.001$ ) and more

favourable to ICU admission (75% vs. 66%;  $P < 0.001$ ). In addition, patients or their surrogates were more involved in the decision making process (49% vs. 24%;  $P < 0.001$ ) and more favourable to admission (88% vs. 66%;  $P < 0.001$ ). ICU admission rate was accordingly higher (61% vs. 34%;  $P < 0.001$ ), which remained significant after adjustment for baseline differences.

Crude six-month mortality was significantly higher in the systematic strategy group (45% vs. 39%;  $P < 0.001$ ; RR, 1.16; 95% CI, 1.07 to 1.26), however, significance was lost after adjustment for baseline differences (RR, 1.05; 95% CI, 0.96 to 1.14). In-hospital mortality (30% vs. 21%;  $P < 0.01$ ; RR, 1.39; 95% CI, 1.23 to 1.57) was significantly higher in the intervention group, which remained after baseline adjustments. Similarly, length of stay was also longer in the intervention group (16.8 vs. 13.6 days; difference 3.2 days; 95% CI, 1.7 to 4.7 days;  $P < 0.001$ ). At 6 months, 28% of intervention and 24% of control patients had an Index of ADL score  $< 4$  (a score  $\geq 4$  at baseline was required for enrolment). Overall 32% of patients were functionally independent (Index of ADL scale = 6) at 6 months compared to 64% at baseline. The decrease in ADL score from baseline was significantly worse in the intervention group {median change, -0.5 (IQR -2 to 0) vs. -0.5 (IQR -1.5 to 0);  $P=0.02$ }. Self reported scores for quality of life at 6 months were similar between groups (mean score for physical QOL 36.7 vs. 36.2; mean score for mental QOL 44.6 vs. 43.7).

The post-hoc analysis of patients admitted to ICU suggested that those in the systematic group had a higher illness acuity and were more often mechanically ventilated (42% vs. 31%;  $P < 0.001$ ). They received NIV (28% vs. 36%;  $P < 0.001$ ) and fluid resuscitation (21% vs. 31%;  $P < 0.001$ ) less frequently. The incidence of vasopressor and renal replacement therapy use did not significantly differ, nor did the number of admitted patients receiving no ICU-specific therapies (19% vs. 14%). There were 49 (1.6%) protocol violations, most commonly due to mis-enrolling a patient with an Index of ADL  $< 4$ .

## Critique

This is a thought-provoking study which builds on previous work by the same group. ICE-CUB1 was a prospective cohort study demonstrated a large variability in admission rates between sites (and presumably individual clinicians) for outwardly similar patients. It also found that it was difficult to identify a survival benefit for those who were admitted to the ICU.<sup>3</sup> The 'ideal' way to test this would be to randomize individual patients to mandated ICU admission or ward care; however, this was clearly impossible due to the restrictions of equity of access to care and physician autonomy. The cluster-randomisation of hospitals allowed the best approximation to these 'ideals' by testing instead a strategy aiming to increase ICU admission rates in intervention sites to allow



comparison of an expanded ICU population against standard care; whilst still allowing for clinician discretion.

There are laudable aspects to the study. The intervention extended to involve the ED physicians as variation in referral to ICU was identified as a potential issue in ICE-CUB1. There was also a multi-faceted approach to encourage compliance with its aims. The exclusion criteria included those associated with a poor outcome in ICE-CUB 1, aiming to avoid asking clinicians to admit those unlikely to benefit. Efforts were made to avoid the 19% incidence of lack of a local ICU bed influencing clinician decisions. Decisions to admit or not admit were followed in all but one case. The chosen primary outcome was of clinical relevance and its assessment was near-complete (one patient withdrew consent). Secondary outcomes were also of clinical interest, and data was collected on the home circumstances of 98% of survivors.

There are some issues to bear in mind when considering the results. Whilst there was a near-doubling of ICU admission rates in the hospitals randomised to the intervention it must be remembered that clinicians still had the final say on admission and 39% of patients in intervention hospitals were not admitted to ICU despite a qualifying condition and a good baseline functional status. Patients were declined both on the basis of being too well and too sick and it should be noted that clinician predictions of ICU mortality are not always accurate.<sup>6</sup> Recruitment was slower in control hospitals, which was probably predictable; the extension of recruitment in this arm balanced study numbers at the expense of the risk of introducing temporal biases and may have been better avoided. It is interesting that there wasn't a higher rate of inter-hospital transfers in the intervention group, despite the higher ICU admission rate and 19% incidence of there being no empty on-site ICU bed, suggesting that local bed availability may have remained an issue effecting admission in this group.

The effect of the intervention was to increase ICU admission rates amongst a highly selected population (estimated to be 33% of those >75 years old with qualifying conditions, equating to 2.6% of overall ED visits amongst >75 years olds). Although this group had the characteristics associated with survival in ICE-CUB1, it could have excluded significant numbers of those in which ICU therapies may have improved outcome. SAPS-III scores were higher in those enrolled in intervention hospital; this may have been a chance finding, however, as there was no ED screening log and no data recorded on eligible patients who weren't enrolled, biases cannot be excluded. 17% of those admitted to ICU received no critical care-specific interventions and it is possible that a difference may have been demonstrated if those patients had been excluded.

Outcomes for the study population as a whole were sobering. At six months, 42% of patients were dead and half of the survivors had lost functional independence. Whilst it is still possible that a trial of true mandated admission may have shown benefit, this trial has not suggested any meaningful benefit from its expanded ICU population (the higher mental QOL scores were clinically insignificant). Indeed, although the increase in crude 6-month mortality was not significant when corrected for illness severity scores, the intervention group patients had higher corrected hospital mortality and length of stay, and a greater decrease in ADL scores, leaving open the possibility of real harm from ICU admission in this population. It could be argued that these results support the ethical validity of a trial of ICU admission in a similar population randomised at an individual patient level, although a lack of clinician equipoise may currently prevent this. The results also affirm the importance of considering the likely longer term survival and functional status of ICU candidates. It is possible that a clinical diagnosis of frailty may help identify those least likely to benefit.<sup>7,8</sup>

### **Where this sits in the body of evidence**

In the absence of randomised controlled trials the major prospective cohort studies examining ICU admission decisions in the elderly are the ICE-CUB1 and Eldicus studies. The evidence otherwise comprises retrospective studies and those examining frailty.

The French prospective multi-centre one-year observational cohort study ICE-CUB1 was published in 2012.<sup>3</sup> Eligible patients were > 80 years old presenting to EDs with an ICU-qualifying condition (as used in ICE-CUB2). 2,646 enrolled patients were included, 655 of which were referred to ICU by the ED physician, 50% of which were accepted into ICU, with reasons for this recorded. All patients were followed-up. Mortality at 6 months was 51%, and was near identical in those admitted or not admitted to ICU. Variables predicting 6-month mortality were those describing general pre-morbid health and functional status. Those triaged by ED or ICU as too sick or too well for ICU admission had an appropriately higher and lower mortality respectively. Rates of ICU admission varied by six-fold between centres; outcomes were not better in centres admitting a greater proportion of those eligible. A Cox model adjusted for age, sex, diagnosis, functional and nutritional status, and illness severity suggested that 6-month survival was poorer for those admitted to ICU (HR, 1.2; 95% CI, 1.01 to 1.43).<sup>9</sup>

The Eldicus-2 study similarly studied the ICU triage process and examined outcomes in the elderly ICU population.<sup>2</sup> 6,796 patients were prospectively enrolled from 11 ICUs in 7 European countries over 2 years. 5,602 (82%) were accepted and 1,194 (18%) declined for ICU admission. Refusal rates and 28-day mortality rose with age (15% refusal and 21% mortality for 45-64 years old vs. 36% and 48% for > 84 years old). Mortality, adjusted for illness severity, was lower in those admitted than refused (in > 65 years old:

OR, 0.65; 95% CI, 0.55 to 0.78;  $P < 0.0001$ ). Declined patients, included those felt clinically to be too unwell to benefit, had a 75% 28-day mortality overall. This 'benefit' of ICU admission was greatest in the elderly and provided evidence for increased acceptance of this population into ICU. The study is limited by the lack of long-term data on mortality, function or QOL and the lack of information on critically ill patients not referred.

Frailty was specifically examined in 3 studies. In a 2014 Canadian prospective cohort study, Bagshaw et al found the presence of frailty {as assessed by a Clinical Frailty Score (CFS)  $> 4$ } was associated with a near-doubling of 1-year mortality of 421 critically ill adults (48% vs. 25%; OR, 1.82; 95% CI, 1.3 to 2.6).<sup>7</sup> Frail survivors were more likely to be functionally dependent and had lower QOL scores. Secondly, in a French prospective study of 196 ICU patients  $> 65$  years old by Le Maguet, frailty (CFS  $\geq 5$ ) was observed in 23%.<sup>8</sup> Frailty was a significant risk factor for 6-month mortality and more strongly predictive than SOFA scores. Lastly, Heyland published a prospective cohort study in 2015 of 1,671 patients aged  $>80$  years admitted to 24 Canadian ICUs.<sup>10</sup> Median ICU length of stay was 4 days. Hospital mortality was 35%, rising to 55% in the subset of frail patients (CFS  $> 5$ ). Non-survivors had a prolonged (median 10 days) ICU stay and 49% died receiving invasive therapies. In a subset of 610 patients with longer follow up, 1-year mortality was 44%, and just 26% of survivors had physically recovered.<sup>11</sup> Outcomes were again worse in frail patients. 17% of the cohort was lost to follow-up.

In 2015 Valley published a retrospective cohort study of  $>1$  million US medicare beneficiaries with pneumonia, 30% of whom were admitted to ICU.<sup>12</sup> Admission rates were higher for those who lived closer to an ICU. The cohort was split and the 13% of patients apparently not admitted on the basis of distance from an ICU was analysed separately. In this group adjusted mortality was lower in those admitted to ICU (14.8% vs. 20.5%; difference -5.7%;  $P = 0.02$ ) and hospital costs were similar.

In contrast, Chang published a retrospective analysis of 156,842 patients admitted to 94 US hospitals with pulmonary embolism, diabetic ketoacidosis, gastrointestinal bleeding or acute heart failure.<sup>13</sup> Logistic regression analysis and ICU billing data suggested there was a wide variation in rates of ICU utilisation for the conditions. Hospitals with higher ICU utilisation had increased costs and use of invasive procedures but no observed difference in hospital mortality.

Bagshaw analysed the Australia and New Zealand Intensive Care Society (ANZICS) database and published a retrospective review of 15,640 elderly ( $> 80$  years old) ICU patients.<sup>14</sup> Admission rates increased by 5.6% per year during the 5 years analysed to comprise 18% of the ANZICS cohort. ICU and hospital mortality were 12% and 24%,

respectively, and was higher for those admitted from a care facility and those with co-morbidities, higher illness severity scores or in receipt of mechanical ventilation. There was no data available on the triage process, long term mortality or functional status.

In 2015 Andersen et al retrospectively reported on 395 patients > 80 years old admitted to their Norwegian ICU between 2000-2012.<sup>15</sup> Survival rates were 76% in the ICU and 42% at 1-year. Health-related QOL of survivors was similar to that of matched controls. Age, ventilation and SOFA score were predictors of ICU but not 1-year mortality. Of note 67% were post surgery (23% elective) and median ICU length-of-stay was 1.8 days.

Sligl et al examined the association between age and outcome in 351 Canadian ICU patients with pneumonia.<sup>16</sup> Overall, mean age was 61, 83% received mechanical ventilation and mortality was 17% at 30 days and 32% at 1 year. Age was an independent risk for 1-year mortality (per 10 years increase; HR, 1.24; 95% CI, 1.03 to 1.49; P = 0.026). Mortality was 57% at 1 year in those ≥ 80 years old.

In 2012 Fuchs et al published a retrospective analysis of 7,265 elderly patients admitted to a Boston ICU, analysed by dividing into 3 age groups. Higher age was an independent predictor of mortality on regression analysis, with 1-year mortality ranging from 36% (65-74 years old) to 56% (>84 years old). The same lead investigator published a retrospective review in 2014 of the same database examining outcomes from elderly (>65 years old) patients admitted over 7 years up to 2008.<sup>17</sup> Admission rates rose by 5.6% per year, with a decrease in illness severity after a new ICU was opened and capacity increased. As hospital mortality and adjusted 1-year survival rates did not improve, the investigators questioned the benefit of increasing ICU admission rates in this population.

### **Should we aim to admit more elderly patients into our ICUs?**

No. Increasing ICU admission rates in this subset of elderly patients did not show any benefit. We should be aware of the impact of critical illness on long term outcomes in this group. The question of whom we should admit to ICU still has no easy answer.

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## Outcome Prediction

**Detsky ME, Harhay MO, Bayard DF, Delman AM, Buehler AE, Kent SA, et al. Discriminative Accuracy of Physician and Nurse Predictions for Survival and Functional Outcomes 6 Months After an ICU Admission. JAMA 2017;317(21):2187–95**

### Introduction

The UK NHS document “No decision about me, without me” tells us that shared decision making is fundamental to good patient care.<sup>1</sup> To achieve this, patients need information about their likely outcomes and treatment options. Yet, accurate prognostication for individual ICU patients is challenging. To determine prognosis, clinicians must take into account the patient’s baseline level of functioning, their co-morbidities, the condition which has led to ICU admission and their acute physiology. One of a multitude of scoring systems can be used to aid prognostication which may be either generic {for example, Sequential Organ Failure Assessment (SOFA) score}, organ specific (for example, Glasgow Coma Scale) or disease specific (for example, Child-Pugh score).<sup>2</sup> A given patient may have a number of scoring systems applicable to their presentation. To assimilate all this evidence is a difficult task.

Even seemingly objective evidence will be interpreted by the clinician in light of their previous experiences caring for critically ill patients.<sup>3</sup> As these cognitive biases are based on prior experience, they are inherently weak in the setting of ICU where outcomes are continuing to improve.<sup>4</sup> For example, physicians may perceive that outcomes from severe sepsis are poor, but between 2000 and 2012, mortality from severe sepsis in Australia and New Zealand almost halved from 35.0% to 18.4%.<sup>5</sup> A similar picture is seen in out-of-hospital cardiac arrest where survival rates have doubled in the past decade.<sup>6</sup>

In light of this, a study examining how accurate physicians and nurses are at predicting long term patient outcome was warranted. This study has the potential to significantly impact shared decision making as patients may wish to know how certain (or not) physicians and nurses are about their prognostications.

### Synopsis

The aim of this prospective study was to ascertain the ability of physicians and nurses to predict outcomes for ICU patients at six months. Patients who were between three and six days (inclusive) into their ICU stay were eligible provided they had received 48 consecutive hours of mechanical ventilation, 24 consecutive hours of vasopressors or both. Neurosurgical or trauma patients, those with an immediate plan for palliation or who were unlikely to be available for follow up were excluded. The study was conducted

in 5 ICUs in the University of Pennsylvania Health System. Consent was obtained from both patients (or their surrogates if they lacked capacity) and physicians and nurses making the prediction.

Each patient’s primary ICU physician (who had been in charge of the patients care for at least two days) and bedside nurse (who had cared for the patient for at least one day) were asked to predict hospital mortality, mortality at six months and ability to return to original place of residence. Assuming the patient was alive at six months, physicians and nurses were asked whether they thought patients would or would not be able to toilet independently, climb 10 stairs independently, and cognate normally. Normal cognition was defined by the investigators as the ability to “remember most things, think clearly, and solve day-to-day problems”. Each participant was asked how confident they were in their prediction on a five point Likert scale ranging not confident at all to very confident. Predictions were made within 24 hours of patient enrolment.

A standardised questionnaire script was used to collect data on patient’s baseline level of functioning and outcomes for those alive at six months. Responses from patients and their surrogates were deemed equivalent. Outcome assessors were blinded regarding the clinicians prediction of outcomes.

Likelihood ratio	Approximate change in probability	Interpretation
0.1	-45%	a positive test means the condition is less likely to be present
0.2	-30%	
0.5	-15%	
1	0	a positive test neither makes the condition more or less likely
2	+15%	a positive test means the condition is more likely to be present
5	+30%	
10	+45%	

**Table 19. Change in probability with likelihood ratio<sup>9</sup>**

*When likelihood ratios are used to describe a test with a dichotomous outcome, positive and negative likelihood ratios are quoted. In the context of this paper, a positive likelihood ratio (sensitivity / 1 - specificity) relates to patients having a poor outcome when predicted to do so, and a negative likelihood ratio (1 - sensitivity / specificity) relates to patients who have a good outcome when predicted to do well.*

The primary outcome measures were positive and negative likelihood ratios (Table 19) and C-statistic for the ability to predict mortality and four functional outcomes at six



months. Likelihood ratios are a measure of diagnostic accuracy and are further discussed in the critique. The investigators assumed that the sensitivity and specificity of predictions used to calculate likelihood ratios would be approximately 75%. They sought to recruit 300 patients, which would give an 80% power to detect 95% confidence intervals < 20% around the sensitivity and specificity of predictions. Secondary outcome measures included likelihood ratios when physicians and nurses were considerably confident or very confident in their prediction.

A total of 303 of the 340 eligible patients or surrogates approached provided consent to participate. A typical patient was a male in their early 60s who was functionally independent. 90.4% were living in their own home prior to admission. A large number of patients had co-morbidities and 70.3% had been hospitalised in the previous year. The two most common admission diagnoses were respiratory failure (27.4%) and sepsis (21.8%). The median APACHE III score was 96 (IQR, 75 - 120). Baseline level of functioning and patient outcomes at six months are shown in table 20. Physicians (n = 47) and nurses (n = 128) were allowed to make predictions on more than one patient. A typical physician making a prediction was a male in their early 40s having graduated 10 to 14 years previously. Nurses were typically female in their late 20s having graduated 5 to 9 years previously.

	Prior to ICU admission (n = 303)	Outcome at 6 months (n = 299)*
In hospital mortality	N/A	23%
Six month mortality	N/A	43%
Unable return to original residence	N/A	53%
Able to toilet independently	88%	82%
Able to climb 10 stairs independently	81%	71%
Cognate normally	81%	62%

**Table 20. Baseline function prior to ICU admission and outcomes**

*\*Values based on patients for whom physicians had made predictions*

Both groups performed best in predicting in-hospital and 6-month mortality (Table 21). Physicians also performed well in predicting ability to toilet independently at 6-months. Both groups performed poorly in predicting ability to cognate normally, climb 10 stairs independently or return to original place of residence. Approximately half of all predictions were rated as considerably confident or very confident; physicians 41-55% of predictions, nurses 44-57% of predictions. When the investigators looked at predictions of outcome where the physician or nurse was considerably confident or very confident,

all positive likelihood ratios appropriately increased and negative likelihood ratios all decreased in value. For example, a positive likelihood ratio of 33.00 (95% CI, 8.34 to 130.63) was seen when physicians were considerably confident or very confident in predicting six month mortality.

The only prediction where one group outperformed the other was the prediction of 6-month mortality; physicians (C-statistic, 0.76; 95% CI, 0.72 to 0.81) vs. nurses (C-statistic 0.69; 95% CI, 0.64 to 0.74, P = 0.02). Both doctors and nurses had a poor ability to predict abnormal cognition at 6 months; C-statistic 0.61 (95% CI 0.54 to 0.68) and 0.55 (95% CI 0.48 to 0.62) for doctors and nurses respectively. For nurses, the lower end of the 95% CI crossed 0.5 which represents a prediction no better than chance.

The range of agreement between the two groups was 69 to 86%. In 86% of cases physicians and nurses agreed in their prediction of mortality (Kappa, 0.49). The highest likelihood ratio was seen where physicians and nurses were concordant in their prediction that a patient would not be alive at six months; positive likelihood ratio, 40.35 (95% CI 5.73 to 284.28). Nurses and physicians were both confident and in agreement in their prediction in 22-33% of their predictions.

	Physicians Predictions		Nurses Predictions	
	Positive LR (95% CI)	Negative LR (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
In hospital mortality	4.81 (2.91-7.95)	0.64 (0.52-0.78)	4.71 (2.94-7.56)	0.61 (0.49-0.75)
Six month mortality	5.91 (3.74-9.32)	0.41 (0.33-0.52)	4.23 (2.71-6.61)	0.56 (0.47-0.68)
Unable return to original place of residence	3.20 (2.21-4.62)	0.49 (0.40-0.60)	2.06 (1.57-2.69)	0.51 (0.40-0.65)
Unable to toilet independently	6.00 (3.18-11.30)	0.51 (0.35-0.75)	2.61 (1.74-3.90)	0.48 (0.30-0.78)
Unable to climb 10 stairs independently	2.18 (1.53-3.11)	0.51 (0.34-0.76)	2.04 (1.48-2.82)	0.48 (0.31-0.74)
Cognate normally	2.36 (1.36-4.12)	0.75 (0.61-0.92)	1.50 (0.86-2.60)	0.88 (0.73-1.06)

**Table 21. Likelihood ratios (LR) for all predictions**

## Critique

This was a thought provoking paper which exemplified the uncertainty in predicting outcomes in ICU patients. The in-hospital mortality of 23.8% reveals a sick cohort of patients, with a mortality comparable to patients with septic shock.<sup>7</sup> The trial was well conducted with just four patients lost to follow up. The patient outcomes which physicians and nurses predicted on were relevant to patients and easy to understand.

The power calculations were based on the assumption that sensitivities and specificities used to calculate the likelihood ratios would be in the range of 75% with confidence intervals no wider than 20%. The sensitivities and specificities actually ranged from 29.0% to 91.3%. Of the 12 sensitivities, none exceeded 75%. Of the 12 specificities, nine met the threshold of 75% with confidence intervals < 20%.

Likelihood ratios warrant further discussion as an understanding of this statistical measure is necessary to put the results into context. A likelihood ratio is a measure of how well a diagnostic test performs (or in this case how successful physicians and nurses are at predicting poor outcomes). Likelihood ratios range from zero to infinity. Ratios > 1 equate to an increase in the probability of an outcome occurring in the setting of a positive test result (or prediction of poor outcome). Whereas, values 0 to 1 equate to a decrease in probability of outcome occurring. Positive likelihood ratios of > 10 or negative likelihood ratios of < 0.1 are considered useful, as this represents a significant shift in the chance of an even occurring.

Likelihood ratios are seldom used in clinical practice as a Fagan nomogram is required to accurately convert to the probability of a disease or outcome occurring.<sup>8</sup> The exact magnitude of increase or decrease in the probability of an outcome occurring depends on pre-test and post-test probability, both of which depend on the prevalence of a condition. It is worth noting that likelihood ratios are less affected by prevalence than sensitivity and specificity. The approximate change in the probability of an outcome occurring is given in table 19. These approximations become inaccurate where pre-test probability is < 10% or > 90%, though in practice this is a moot point as this represents areas where a clinician is certain about a diagnosis or when outcomes are easy to predict.<sup>9</sup>

In this investigation, only two positive likelihood ratios exceeded five which represents a modest increase in the chance of a poor outcome. In other words, patients whose physician predicted an outcome of mortality at six months had approximately a 30% relative increase in chance of dying. The same is true of physicians' predictions of inability to toilet independently at six months. The remaining four physician predictions

and six nurse predictions fared even worse than this, with each associated with approximately a 15% to 30% relative increase in chance of a poor outcome.

The investigators comment that in all six physician predictions, the 95% confidence intervals for positive and negative likelihood ratios exclude 1.0. Therefore, physicians have a better than fifty-fifty chance at correctly predicting poor outcomes. Surely the threshold which we use to make predictions on patient outcomes must be much higher than “better-than-chance”. Analysis of data from the ETHICUS study reveals that 79.3% of end of life discussions are initiated by ICU physicians, a further 2.1% are initiated by ICU nurses and just 4.5% initiated by patients or their surrogates.<sup>10</sup> It would seem that patients and their surrogates are heavily reliant on the assessment of physicians and nurses in relation to prognosis and end of life care. When only confident predictions were examined, positive and negative likelihood ratios were higher. However, only two of the 12 quoted positive likelihood ratios where physicians and nurses made confident predictions exceeded 10, which equates to a 45% relative increase in the chance of a poor outcome occurring.

Outcome prediction models are designed for use in large cohorts of ICU patients but are of limited utility when trying to predict outcomes in an individual patient. Studies have shown that the use of models to predict ICU mortality which include patient age, sex, acute physiology score {derived from Acute Physiology And Chronic Health Evaluation II (APACHE II) score} and Charlson co-morbidity index have likelihood ratios as high as 134.<sup>11</sup> In this study, patients who had an ICU stay of < 3 days and who were deemed easier to prognosticate upon were excluded. In the resulting patient cohort, mathematical models outperformed physicians and nurses in predicting poor outcomes. The C-statistic for the model used (which included age, APACHE II, functional co-morbidity index, medical vs. surgical admission and hospitalisation in the year prior to ICU admission) ranged from 0.654 to 0.803 in comparison to 0.55 to 0.76 for predictions made by physicians and nurses.

The range of agreement between the physicians and nurses was 69 to 86%. This probably represents uncertainty in relation to outcomes as opposed to disagreement between the two groups per se. When the demographics of physicians and nurses were compared, nurses were younger, had fewer years clinical experience and had spent less time with the patient they were asked to make predictions on. Yet, in only one aspect did physicians outperform nurses. Physicians were more accurate in their prediction of 6-month mortality. Although this was statistically significant, in practice the C-statistics were similar and therefore it would seem to be of little clinical relevance. Furthermore it could be argued that physicians have greater influence over decisions regarding withdrawal of life sustaining treatments. Physicians and nurses who made predictions

were also involved in decisions regarding continuing or withholding life sustaining treatment, this may have introduced a considerable confounding variable especially in relation to confident predictions.

What we can learn from this thought provoking study is that physicians and nurses are relatively poor at predicting outcomes (and are outperformed by mathematical models). It would seem incumbent upon us to be honest with our patients and their surrogates about any uncertainty. Crucially though, greater confidence in predictions and agreement between physicians and nurses brings greater certainty about outcomes. Thus, a consensus opinion about the likelihood of a poor outcome carries great weight. The value comes from physicians and nurses putting these potential outcomes in context for the patient having taken on board their wishes, cultural beliefs and religious views. No mathematical model can replace clinicians in this regard.

### **Where this sits in the body of evidence**

A prospective study of 172 surrogate decision makers for 142 mechanically ventilated patients used semi-structured interviews to examine factors affecting perception of prognosis. Two percent of surrogates based their perception of prognosis solely based upon physician information and a further 47% took physician views into account. A number of themes were identified that influenced surrogates perception of prognosis; the patient's personality or will to live (27%), their physical appearance (64%), prior survival of serious illness (28%), the presence of a surrogate at the patient's bedside (13%), and faith (20%).<sup>12</sup>

An analysis of 51 audiotaped consultations between ICU physicians and patients surrogates was carried out. Cases were selected where physicians planned to discuss withdrawal or withholding life sustaining treatment. The group of patients included had an ICU mortality of 80%. In 96% of cases there were discussions about withdrawal of life sustaining therapies or do not attempt cardiopulmonary resuscitation orders. In 63% of cases chances of survival were discussed, and likely functional outcomes were discussed in 86% of cases.<sup>13</sup>

In an effort to derive a mortality prediction model 24,508 ICU cases from a single centre were examined. The investigators compared how well a new "Super Learner-based" mortality prediction algorithm compared to pre-existing models. The AUROC (area under receiver operating characteristic) for SOFA score was 0.71 (95% CI, 0.70 to 0.72), 0.78 for SAPS-II score (95% CI, 0.77 to 0.78), and 0.88 (95% CI, 0.87 to 0.89) for the Super Learner-based algorithm. This algorithm was subsequently validated in a small cohort of patients (n = 200) from a French ICU.<sup>14</sup>

A cohort of 260 patients who had been ventilated in ICU for 21 days were examined to identify risk factors for 1 year mortality. A weighting was applied to four variables to derive a prediction model; age (years), platelet count, vasopressors (yes / no), and hemodialysis in the last 48 hours (yes / no). The AUROC for this model was 0.79 (95% CI, 0.75 to 0.81). This compared favourably with APACHE III score (AUROC, 0.63). In a simplified model, where patients scored points for age ( $\geq 65$  yrs, 2 points; 50 to 64 yrs, 1 point), platelet count ( $\leq 150 \times 10^9/L$ , 1 point) vasopressor dependence (1 point) or hemodialysis in the last 48 hours (1 point), a score of  $> 2$  correlated with an 86% one year mortality.<sup>15</sup>

In 1991, the APACHE III scoring system was published. Data on 17,440 patients from 40 hospitals was used, with half of patients contributing to a derivation cohort and half to a validation cohort. The APACHE III score in the first 24 hours accurately predicted mortality within an AUROC of 0.90.<sup>16</sup>

### **Should we tell patients about our confidence in our estimates of prognosis?**

Yes, this should form part of shared decision making with patients or their surrogates.

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# **Section 2:**

# **The Best of the Rest**

# **2017**





# Neuro Trials



## DEXILIRIUM

**Deiner S, Luo X, Lin H, Sessler D, Saager L, Sieber F et al. Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery - A Randomized Clinical Trial. JAMA Surg 2017;152(8):e171505**

Whether peri-operative delirium and post-operative cognitive dysfunction (POCD) is causal in the development of poor long term outcomes, or is simply a marker of frailty, is debated. As post-operative use of the  $\alpha_2$  adrenergic agonist dexmedetomidine reduces delirium rates post cardiac surgery, when compared to propofol,<sup>1</sup> the DEXILIRIUM investigators hypothesised intra-operative use may reduce delirium and POCD rates.

Eligible patients were > 68 years old, without pre-existing dementia and undergoing major elective non-cardiac surgery under general anaesthesia. Those with pre-existing dementia, a life-limiting diagnosis, for emergency surgery or with a contraindication to the study drug were excluded. Patients were randomised to receive an infusion of dexmedetomidine (0.5  $\mu\text{g}/\text{kg}/\text{h}$ ) or matching saline placebo from arrival in theatre to 2 hours post-operatively. Investigators and clinicians were blinded. Anaesthesia was maintained with propofol or sevoflurane, with opioids at the discretion of the anaesthetist. Benzodiazepines were not permitted. The study was powered to detect a 50% decrease in the incidence of delirium, from an assumed 15% in the placebo group.

404 patients were randomised over 6 years before the study was stopped for futility in 2014. Nine did not receive the allocated treatment. The median age was 74 years old, median anaesthetic time was 253 minutes, 84% of operations were general, orthopaedic or spinal surgery. Delirium was diagnosed in-hospital in 11.8% of patients. Rates did not differ between groups (primary outcome; 12.2% of dexmedetomidine group vs. 11.4% of placebo; RR, 1.06; 95% CI, 0.79 to 1.41;  $P = 0.77$ ). There was no difference in subtype or severity of delirium between groups. There was also no difference in the age-adjusted cognitive performance at 3 or 6 months (secondary outcome). Bradycardia requiring treatment occurred in 35 & 20 patients in the intervention & placebo groups, respectively ( $P=0.06$ ). There were less postoperative infections in the placebo group.

### **Should we reach be asking anaesthetists to give intra-operative dexmedetomidine?**

No. There was no benefit from dexmedetomidine as used in this study.

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## DAWN

**Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. N Engl J Med 2018; 378:11-21**

Although it is now well described that early endovascular thrombectomy in acute ischaemic stroke is beneficial when undertaken within 6 hours of onset, it is less clear if this also applies after this time point. Evidence from non-randomised trials suggests patients suffering from ischaemic symptoms which appear disproportionately large in comparison with the volume of infarcted tissue on CT scanning could benefit from delayed thrombectomy.

DAWN was an international, open-label, multi-centre, randomised controlled trial, with a Bayesian adaptive-enrichment design, comparing thrombectomy plus standard care to standard care alone. Patients were suitable if they had, within 24 hours of onset, evidence of occlusion of the intracranial internal carotid artery, the first section of the middle cerebral artery, or both on CT angiography or MR angiography, and they had a mismatch between imaging and clinical severity of stroke, in addition to an absence of haemorrhage and a good premorbid level of function.

206 patients were enrolled over a 2.5 year period, with 107 in the thrombectomy group and 99 in the standard care group. Groups were well matched at baseline, including a NIHSS (severity of stroke deficit) score of 17 each. The median time between onset of symptoms and randomisation was 12.2 and 13.2 hours in the thrombectomy and standard care groups, respectively. 105 of the 107 patients in the thrombectomy group received thrombectomy.

For every 2 patients who underwent thrombectomy, 1 patient had less disability at 90 days compared with the control group. For every 2.8 patients who underwent thrombectomy, 1 more had functional independence at 90 days than in the control group. 82% to 84% of the thrombectomy group had immediate reperfusion. Recanalisation was achieved in 77% at 24 hours. There was no difference in safety endpoints.

**Should stroke patients be offered thrombectomy up to 24 hours post onset.**

Probably, although further studies are required to confirm these findings.

# Circulatory Trials



## Tracheal Intubation during Cardiac Arrest

**Andersen LW, Granfeldt A, Callaway CW, Bradley SM, Soar J, Nolan JP, et al. Association Between Tracheal Intubation During Adult In-Hospital Cardiac Arrest and Survival. JAMA 2017;317(5):494–506**

This retrospective, observational study examined the effect of tracheal intubation during in-hospital cardiac arrest (IHCA) on survival. Patient data was collected from the US-based, multi-centre Get With The Guidelines–Resuscitation (GWTG-R) registry. Patients aged  $\geq 18$  years who suffered an IHCA between 2000 and 2014 were included. Those intubated with an endotracheal tube or tracheostomy within the first 15 minutes of their IHCA were compared to similar controls. Patients were excluded if they had an endotracheal tube, tracheostomy or laryngeal mask airway in situ at the time of their cardiac arrest.

Survival to hospital discharge was the primary outcome measure. Secondary outcomes were return of spontaneous circulation (ROSC) for  $> 20$  minutes and favourable neurological outcome at hospital discharge (cerebral performance category score of 1 or 2). A Cox proportional hazards model was used to create a propensity score and match intubated patients with controls. Time-dependent propensity score matching was used. Patients who were intubated had their time of intubation recorded and were compared to controls who were *at risk* of intubation at the same time point. Thus, controls were unintubated and still receiving resuscitation but may have been intubated at a later point and became “cases” themselves.

There were 108,079 eligible patients with a full data set. 58% were male, the median age was 69 years (IQR, 58 - 79 years), and 36% were in ICU at the time of cardiac arrest. For those intubated within the first 15 minutes, the median time to intubation was 5 minutes (IQR, 3 - 8 minutes). 43,314 intubated patients (exposed group) were matched with 43,314 controls (unexposed group). The groups had similar baseline and cardiac arrest characteristics. In the unexposed group, 68.2% went on to be intubated at a later point. Survival to hospital discharge was lower in the exposed group (16.3% vs.19.4%; RR, 0.84; 95% CI, 0.81 to 0.87;  $P < 0.001$ ). ROSC was less common in the exposed group (RR, 0.97; 95% CI, 0.96 to 0.99;  $P < 0.001$ ) as was favourable neurological outcome (RR, 0.78; 95% CI, 0.75 to 0.81;  $P < 0.001$ ). In prespecified sub-group analysis, intubation was associated with decreased survival in both those with a shockable rhythm (RR, 0.68; 95% CI, 0.65 to 0.72) and a non-shockable rhythm (RR, 0.91; 95% CI, 0.88 to 0.94).

### **Should we intubate during in-hospital cardiac arrest?**

Possibly. Associative studies suggest harm from intubation, but causation remains undetermined. These registry-based studies are at significant risk of inherent bias.

## Noradrenaline Shortage

**Vail E, Gershengorn HB, Hua M, Walkey AJ, Rubenfeld G, Wunsch H. Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock. JAMA 2017;317(14):1433–42**

In 2011, the US suffered a nationwide shortage of noradrenaline. The Premier Healthcare Database was retrospectively examined to ascertain if there was an association between mortality from septic shock and admission during the noradrenaline shortage. Data for each 3 month period (quarter) from 2008 to 2013 was analysed. Data from July 2008 to June 2010 was used to establish the baseline rate of vasopressor use in septic shock. "Shortage hospitals" were those which:

- demonstrated a 20% reduction in noradrenaline use in any quarter in 2011
- subsequently returned to within 10% of baseline noradrenaline use by 2012
- excluding 2011, had no other quarter where noradrenaline use fell by > 20%

Patients with septic shock during a "shortage quarter" represented the cohort. They were compared to patients who received care in "shortage hospitals" outside a period of shortage and to patients in "consistent-use hospitals" where there was never a noradrenaline shortage. The association between admission during a "shortage period" and in-hospital mortality was examined using mixed effects logistic regression analysis.

Data on 584,421 patients with septic shock from 532 hospitals was screened for eligibility. After exclusions of ineligible patients and hospitals, 102 hospitals met the definition of a consistent-use hospital (120,759 patients) and 26 hospitals of a shortage hospital (27,835 patients). 1,961 patients (7.0%) were admitted during a shortage quarter. The cohort and control groups were well matched. A typical patient was a white male in their late 60s. The baseline noradrenaline use was 78.5% (95% CI, 78.2% to 78.7%). In shortage hospitals, during the shortage quarters the use of noradrenaline fell significantly (50.8% vs. 79.9), whereas the use of other vasoactive agents increased significantly: phenylephrine (55.1% vs. 36.6%), dopamine (48.6% vs. 40.5%) and vasopressin (31.7% vs. 25.6%) (all  $P < 0.001$ ). Within shortage hospitals, in-hospital mortality from septic shock was significantly higher during shortage quarters (39.6%) than non-shortage quarters (35.9%), (adjusted odds ratio, 1.15; 95% CI, 1.01 to 1.30;  $P = 0.03$ ). When mortality in the cohort was compared to mortality in consistent use hospitals in 2011, an increase in in-hospital mortality was observed (AOR, 1.17; 95% CI, 1.06 to 1.31;  $P = 0.003$ ). This suggests the increase in mortality was associated with noradrenaline shortage and not due to trends over time.

### **Why is lower noradrenaline use associated with increased mortality?**

This may be due to harmful effects of alternate vasopressors or changes in patient care.

## DETO2X-AMI

**Robin Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N. Oxygen Therapy in Suspected Acute Myocardial Infarction. N Engl J Med 2017;377:1240-1249**

Oxygen therapy has come under increasing scrutiny over the past several years, with trials demonstrating harm in the setting of stroke, cardiac arrest, ARDS, mechanical ventilation and myocardial infarction. In particular, as a vasoconstrictor, supplemental oxygen has the potential to exacerbate coronary ischaemia. However, these earlier trials may lack suitable power, endpoints or robustness to solidify these findings. DETOX-AMI was a Swedish multi-center, open-label, registry-based, randomized, controlled trial, comparing routine supplemental oxygen with ambient air in non-hypoxaemic patients with acute myocardial infarction.

Eligible patients were older than 30 years, have ischaemic symptoms for less than 6 hours, have an SpO<sub>2</sub> ≥ 90% and either ECG or troponin evidence of acute myocardial infarction. Those requiring supplemental oxygen were excluded. Those randomised to supplemental oxygen received this through a facemask at 6 L/min for 6 to 12 hours. Supplemental oxygen could be administered to the control group if they became hypoxic. 6,600 patients were required to identify a 20% relative mortality reduction at 1 year in the oxygen group, from a control group baseline of 14.4%. (β, 0.9; α, 0.05).

6,629 were randomised, with a median time from onset of symptoms to randomisation of 245 and 250 minutes, in the oxygen and control groups, respectively. 75.6% were subsequently diagnosed as having an acute myocardial infarction. Groups were similar at baseline, received equivalent therapies and separated well with respect to oxygen exposure. Just 4.8% received supplemental oxygen outside of the trial. 6% did not complete the trial, most often due to a refusal to wear the oxygen mask.

In the intention-to-treat analysis, there was no difference in 1 year mortality; oxygen group, 5.0% vs. control group, 5.1%; HR, 0.97; 95% CI, 0.79 to 1.21; P = 0.80). This finding was unchanged in the per protocol analysis. Rehospitalisation due to recurrent acute myocardial infarction within 1 year occurred in 3.8% and 3.3% of the oxygen and control groups, respectively (HR, 1.13; 95% CI, 0.88 to 1.46; P = 0.33). There was no difference in 30-day mortality.

**Should we routinely administer supplemental oxygen to patients with an MI?**

No. These data further support the view of administering oxygen only when necessary.

## TRUE-AHF

### **Packer M, O'Connor C, McMurray J, Wittes J, Abraham W, Anker S et al. Effect of Ularitide on Cardiovascular Mortality in Acute Heart Failure. NEJM 2017; (376):1956-64**

The RELAX-AHF trial suggested that the vasodilator serelaxin may reduce cardiovascular mortality in acute heart failure, potentially by attenuating ventricular distension and cardiac wall stress.<sup>1</sup> Ularitide is a synthetic analogue of urodilatin with natriuretic and vasodilator properties which had promising physiological effects in small studies. In TRUE-AHF 2,157 adults, from 23 countries, with both clinical and serum {raised N-terminal pro-Brain Natriuretic Peptide (NT-proBNP)} evidence of acute heart failure, persisting after intravenous diuretics and a systolic blood pressure (SBP) of 116-180 mm Hg, were randomised to 15 ng/kg/min ularitide (n = 1,088) or matching placebo (n = 1,069) for 48 hours. 29 did not receive the study drug. At study entry, intravenous nitrates were used in 10%, dobutamine in 0.5%, 65% had a left ventricular ejection fraction of <40% and median NT-proBNP was  $\approx$  7,130 pg/ml. Groups were well matched.

There was no difference in the co-primary endpoints of cardiovascular death at any stage (21.7% vs. 21.0%; hazard ratio, 1.03; 96% CI, 0.85 to 1.25; P = 0.75) or composite clinical outcome (a comparison of number of patients improved, unchanged or worse by 48 hours; P = 0.82). Ularitide demonstrated physiological effect, with a greater decrease in SBP (6.8 mm Hg mean difference at 6 hours; P < 0.001), with discontinuation of infusion in 12%, and a small rise in haematocrit and serum creatinine, which may reflect haemoconcentration. It was otherwise well tolerated. There was a greater fall in NT-proBNP at 48 hrs with ularitide (median -3,816 vs. -2,595 pg/ml; P < 0.001) which may reflect reduced cardiac wall stress, however troponin T was unaffected. ICU length of stay was also unaffected, but of note, only 26 patients (1.2%) had received level-3 interventions (vasopressors, invasive ventilation or renal dialysis) by 48 hours. All-cause mortality or cardiovascular death at defined timepoints was not reported.

#### **Should we reach for ularitide for ICU patients in acute heart failure?**

No. There was no outcome benefit seen and these were inpatients without overt end-organ failure who would not be representative of those in many ICUs.

1. Teerlink JR, Cotter G, Davison BA, et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *The Lancet* 2013;381(9860):29–39.



## VISION

### **Devereaux PJ, Biccard BM, Sigamani A, Xavier D, Chan MTV, Srinathan SK, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. JAMA 2017;317(16):1642–51**

Myocardial injury after non-cardiac surgery (MINS), defined using non-high sensitivity troponin assays, is associated with an increase in perioperative mortality. This international, observational study sought to determine the association between high-sensitivity troponin T (hsTnT) after non-cardiac surgery and 30-day mortality. Statistical analysis was performed to ascertain if a threshold hsTnT could predicted a three-fold increase in 30-day mortality or a mortality  $\geq 3\%$ . Patients aged  $\geq 45$  years, who underwent inpatient non-cardiac surgery under general or regional anaesthesia, were eligible. Samples were taken for hsTnT between 6 and 12 hours post operatively and then for 3 subsequent days. A proportion of patients also had hsTnT measurements pre-operatively. In unblinded institutions, where hsTnT exceeded 14 ng/L, patients were reviewed for clinical or electrocardiographic evidence of ischaemia.

Over 5 years, 21,842 participants were enrolled from 13 countries. Patients had a mean age of 63.1 (SD, 10.7) years and underwent a wide range of surgery including, low-risk general (35%), major general (20%), and major orthopaedic (16%). The overall 30-day mortality was 1.2% (95% CI; 1.1% to 1.4%). Patients with a peak hsTnT  $< 5$  ng/L were used as a reference group. Table 22 shows the absolute 30-day mortality and hazard ratios for death associated with increased hsTnT. Patients with a rise of hsTnT of  $\geq 5$  ng/L had an absolute 30-day mortality of 3.0% (adjusted HR, 4.69; 95% CI; 3.52 to 6.25). MINS was defined at a hsTnT  $> 65$  ng/L or 20 - 64 ng/L with a change  $\geq 5$  ng/L. MINS without and with ischaemia was associated with a 30 day mortality of 2.9% & 8.5%, respectively.

<b>Peak post operative hsTnT</b>	<b>30 day mortality (95% CI)</b>	<b>Hazard ratio for mortality (95% CI)</b>
20 - 64 ng/L	3.0% (2.6% to 3.6%)	23.63 (10.32 to 54.09; P < 0.001)
65 - 999 ng/L	9.1% (7.6% to 11.0%)	70.34 (30.60 to 161.7;; P < 0.001)
$\geq 1,000$ ng/L	29.6% (19.1% to 42.8%)	227.01 (87.35 to 589.92; P < 0.001)

**Table 22. Post operative hsTnT and mortality risk**

#### **What is the significance of raised hsTnT perioperatively?**

Elevated hsTnT is associated with increased mortality; however, it is unclear if this can be modified.

# Airway Trials



## Check-UP 1: Intubation Checklist

**Janz D, Semler M, Joffe E, Casey J, Lentz R, Bennet P et al. A Multicenter Randomized Trial of a Checklist for Endotracheal Intubation of Critically Ill Adults. Chest 2017; published September 13th**

Endotracheal intubation in critical care is a high-risk event.<sup>1</sup> Advocates of checklists can point to evidence of reduced complications from their use in operating theatres, although evidence from ICUs is less impressive.<sup>2,3</sup> In this 12 month study, adults from four American tertiary ICUs requiring intubation were block-randomized to the use of an investigator-derived 10-item pre-intubation checklist or usual care. Clinicians and independent assessors were not blinded. The primary outcomes were the lowest oxygen saturation (SpO<sub>2</sub>) and systolic blood pressure (SBP) within 2 minutes of induction. 260 patients were required to provide 80% power to detect a 5% difference in SpO<sub>2</sub> / 10 mm Hg difference in SBP, at a 5% significance level.

318 patients were intubated during the study period. 56 were excluded (including 43 as too urgent and 5 post-randomisation, when intubation was performed by a nurse). The intention-to-treat analysis included 262 patients, with 130 in the checklist group. Although all patients received the correct intervention, the checklist was incomplete in 19%, most often due to omission of the difficult airway assessment. Baseline characteristics were similar: median age was 57 years & 63% were male. The reasons for intubation were hypoxaemia (56%), hypercarbia (17%) and altered mental status (38%).

There was no difference in either the primary outcome (median, IQR) of lowest SpO<sub>2</sub>: checklist group, 92% (79% - 98%) vs. usual care group, 93% (84% - 100%); P = 0.27; or median lowest SPB: 112 mm Hg (94 - 133) vs. 108 mm Hg (90 - 132); P = 0.61. Results were unaffected by adjustment for patient or operator characteristics. No effect on secondary endpoints, including airway management metrics, complications or patient outcomes, was seen. A potential confounder is that clinicians may have used (but not documented) checklist components when intubating those in the control group. Of note, the investigators studied the effect of intubating position concurrently (*next review*).

### Should we use a checklist when intubating those in ICU

Perhaps. This study has not excluded a benefit of using a different checklist in our own institutions. A much larger study may be required to show an effect on clinical outcomes.

1. Cook TM, Woodall N, Harper J, Benger J. Fourth National Audit Project of the Royal College of Anaesthetists. Part 2: intensive care and emergency departments. *Br J Anaesth* 2011;106(5):632-42
2. 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
3. CHECKLIST-ICU Investigators. Effect of a Quality Improvement Intervention With Daily Round Checklists and Clinician Prompting on Mortality of Critically Ill Patients: *JAMA* 2016;315(14):1480

## Check-UP 2: Intubation Positioning

**Semler M, Janz D, Russell D, Casey J, Lentz R, Zouk A et al. A Multicenter, Randomized Trial of Ramped Position vs Sniffing Position During Endotracheal Intubation of Critically Ill Adults. Chest 2017;152(4):712-722**

Traditional anaesthetic teaching advocates the “sniffing the morning air” position (SP; torso supine, neck flexed, head extended) for optimal direct laryngoscopy during intubation. The ramped position (RP; 25° head of bed elevation) may delay hypoxaemia by increasing functional residual capacity, and was associated with improved glottic view in operating theatres.<sup>1</sup> This study, investigating critically ill adults requiring intubation, ran over 12 months in four American tertiary ICUs. Patients were block-randomized by computer to the SP or RP, with allocation retrieved from a sealed envelope. Clinicians and independent assessors were not blinded. The primary outcome was the lowest oxygen saturation (SpO<sub>2</sub>) within 2 minutes of induction. 260 patients were required to provide 80% power to detect a 5% difference between groups, at a 5% significance level. The primary analysis was by intention-to-treat.

311 patients were intubated during the study period, 49 were excluded (43 too urgent and 6 no clinician equipoise). The remaining 260 were equally allocated to the SP or RP. Baseline characteristics were similar: median age was 56 years, 61% were male, 32% had a BMI > 30 kg/m<sup>2</sup>. The reasons for intubation were hypoxaemia (58%), hypercarbia (15%) and altered mental status (36%). The commonest used drugs were etomidate (90%), succinylcholine and rocuronium (each used in 50%). Intubation was by direct laryngoscopy in 75% and video laryngoscopy in 25%. Three patients were intubated in the non-allocated position. There was no difference in the primary outcome (median; IQR) SP, 92% (79% - 98%) vs. RP, 93% (84% - 99%); P= 0.27. There were no significant differences in pre-specified secondary endpoints of oxygenation, haemodynamic or clinical outcomes, or adverse events. SpO<sub>2</sub> < 70% was recorded in 19 (SP) vs 12 (RP) patients (NS). The SP was significantly better for operator-reported Cormack-Lehane view (grade III or IV view, 11.5% vs. 25.4%, P = 0.01); intubation on first try (85.4% vs. 76.2%; P = 0.02) or need to switch laryngoscopes (6.2% vs 16.2%; P = 0.01). Of note the investigators studied the effect of an intubation checklist concurrently (*previous review*).

### **What is the optimal position for intubating critically ill patients?**

These results favour the sniffing position, although a larger sample may still find an oxygenation benefit from ramping, or could investigate a combination of the two.

1. Lee J-H, Jung H-C. Comparison of the rate of successful endotracheal intubation between the “sniffing” and “ramped” positions in patients with an expected difficult intubation: a prospective randomized study. Korean J Anesthesiol 2015;68(2):116-21

## VL vs. DL for Paramedic Intubation

**Ducharme S, Kramer B, Glebart D, Colleran C, Risavi B, Carlson J. A pilot, prospective, randomized trial of video versus direct laryngoscopy for paramedic endotracheal intubation. *Resuscitation* 2017;114:121–126**

Endotracheal intubation in critical care is a high-risk event.<sup>1</sup> Video laryngoscopes can improve glottic view, although how this translates to improved intubation success rates is less certain. This quasi-randomised, non-blinded crossover trial compared the new King Video Laryngoscope (KVL, Ambu, Denmark) with direct laryngoscopy (DL, Macintosh or Miller blades) in prehospital intubations by two Pennsylvanian (USA) Emergency Medical Services (EMS). Intubations were performed by paramedics, some of which were allowed to use sedation, but not neuromuscular blocking agents (NMBAs). The assignment was by ambulance base, each crossing over to using the other device as first preference for the initial attempt at intubation every 6 months. After this, paramedics were free to change laryngoscope or use a supraglottic airway instead. Training sessions were undertaken for both laryngoscopes.

100 patients were required to have 80% power to detect a 20% increase in successful first attempts (from 65% to 85%). This was expected to take 12 months but after 34 months, 82 out of 88 assessed patients had been recruited and the study was halted for futility. All six excluded did not have attempted intubation.

All but two patients were intubated following cardiac arrest (medical cause in 95%, traumatic in 5%). 42 patients were randomised to DL, but the KVL was used initially in five of these. 75% were male, 57% were > 70 years old, and 45% had an estimated weight > 100kg. There were no differences in the primary outcome of first intubation success (DL, 66.7% vs. KVL, 62.5%; difference, 4.2%; 95% CI, -16% to 23.9%; P = 0.69), overall success (DL, 81% vs. 72.5%, KVL; P = 0.37), laryngoscopy visual grading, or when cross-over patients were excluded. The KVL device was changed after 3 occurrences of failed passage of ET tube through a channeled blade. Excluding these patients did not change the analysis. Most providers intubated ≤ one patient / year.

### **Should this study change my practice when intubating ICU patients?**

No. It should be seen as relevant to infrequent practitioners intubating patients in cardiac arrest in the out-of-hospital setting, without drugs and with the specific King Video Laryngoscope.

1. Cook TM, Woodall N, Harper J, Benger J. Fourth National Audit Project of the Royal College of Anaesthetists. Part 2: intensive care and emergency departments. *Br J Anaesth* 2011;106(5):632–42

# Respiratory Trials



## Gravity-VAP

**Li Bassi G, Panigada M, Ranzani OT, Zanella A, Berra L, Cressoni M. Randomized, multicenter trial of lateral Trendelenburg versus semirecumbent body position for the prevention of ventilator-associated pneumonia. Intensive Care Med 2017;43(11):1572-1584**

Ventilator-associated pneumonia (VAP) is a common and serious problem for intubated patients. A number of interventions have been undertaken to prevent this from occurring, including the use of the semirecumbent position to minimise the risk from gastric aspiration. Contrary to this approach, the Trendelenburg position would theoretically allow secretions to drain away from the larynx and into the oropharynx. There is also evidence that lateral positioning reduces the risk of VAP.

Bassi and colleagues performed a multi-centre, randomised trial in 18 ICUs, comparing a lateral Trendelenburg position (LTP), including frequent turns to the other side, with usual care, in the semirecumbent position at 30° headup. Eligible patients were adults expected to be mechanically ventilated for ≥ 48 hours and within six hours of intubation. Staff received a one day training course prior to study commencement. The patient was assessed each day for suitability for lightening of sedation. A VAP was diagnosed as the presence of a new pulmonary infiltrate, plus 2 of new purulent secretions, temperature above 38°C or less than 35°C; a white cell count > 10 × 10<sup>3</sup> or < 4 × 10<sup>3</sup> per cubic millimeter; in a patient ventilated for > 48 hours. The primary study outcome was the incidence of VAP within the first 14 days, which was confirmed by quantitative bronchoalveolar lavage or mini-BAL cultures of at least 10<sup>4</sup> colony-forming units.

800 patients were required to identify a 50% reduction in the primary outcome, from 15% to 7.5%, with 90% power at a 5% significance level. 2,156 patients were screened and 401 were enrolled, after which the trial was stopped for futility, due to a low incidence of VAP. The groups were similar at baseline. 11.9% of patients in the LTP, and 3.5% of patients in the semirecumbent position were not managed in their allocated position. This was further limited by patients in the LTP only being managed in this position for 30% of the time. There were less cases of VAP with the LTP position (n = 1 vs. n = 8; 0.5% vs 4.0%; RR, 0.13; 95% CI, 0.02 to 1.03). There were no differences in secondary outcomes, although adverse events, such as vomiting, were more frequent in the LTP group.

### **Should we routinely position patients in the LTP to prevent VAP?**

Not at this time. Although interesting, this trial finished early and requires confirmation in a second trial

## RECONNECT

**Fernandez M, González-Castro A, Magret M, Bouza T, Ibañez M, Garcia C et al. Reconnection to mechanical ventilation for 1 h after a successful spontaneous breathing trial reduces reintubation in critically ill patients: a randomized controlled trial. *Intensive Care Med* 2017;43:1660-1667**

A spontaneous breathing trial (SBT) is commonly used to assess suitability for tracheal extubation, but increases cardio-respiratory work and may lead to fatigue. This study tested whether an hour of rest after a SBT avoided reintubation in patients from 17 Spanish ICUs. Eligible patients had received >24 hours ventilation and successfully passed a SBT. The rest group were reconnected to the ventilator at the prior settings for one hour before extubation; control patients were immediately extubated. Excluded were: children, those unresponsive, those with a tracheostomy, severe secretions, a do-not-reintubate order or planned non-invasive ventilation (NIV). Weaning and physiotherapy protocols varied between centres. Randomisation was stratified by centre and assessed risk of failure. The intervention was unblinded but data-collectors were excluded from clinical decision-making.

The primary endpoint was reintubation within 48 hours. 1,372 patients were required to detect a 5% decrease from a 15% reintubation rate (80% power,  $\alpha=0.05$ ); however, by error recruitment ceased after 470 patients were randomised, (227 rest group, 243 control). None were lost to follow-up. A typical patient was male, 62 years old and been ventilated for 5.5 days. 41% were post surgery or trauma and 59% medical. 85% were assessed as high-risk for extubation failure. SBT was by open T-tube in 90%, with pressure support or CPAP in the remainder, the duration of SBT varied from 30 to 120 minutes (120 minutes was more common in control patients, 32% vs. 21%;  $P = 0.009$ ).

Nine rest patients did not tolerate reconnection to the ventilator. The intervention was successful in reducing 48-hour reintubation rates (primary outcome, 5% vs. 14%; OR, 0.33; 95% CI, 0.16 to 0.65;  $P < 0.001$ ). Control patients were also more likely to have post-extubation respiratory failure (24% vs. 10%;  $P < 0.001$ ); NIV prevented reintubation in 66% of those receiving it. There were no differences in length of stay in ICU or hospital, nor mortality. Caveats include the longer SBT in control patients, unintentional underpowering, lack of effect on patient outcomes and no insistence on a single weaning protocol, standardised SBT or use of high-flow nasal oxygen post extubation.

### **Should we rest patients after a SBT and before extubation?**

Yes – With the above noted this was an elegant demonstration of a simple way to reduce the undesirable risk of tracheal reintubation.



## HFNO in Cardiogenic Pulmonary Oedema

**Makdee O, Monsomboon A, Surabenjawong U, Praphruetkit N, Chaisirin W, Chakorn T, et al. High-Flow Nasal Cannula Versus Conventional Oxygen Therapy in Emergency Department Patients With Cardiogenic Pulmonary Edema: A Randomized Controlled Trial. *Annals of Emergency Medicine* 2017;70(4):465-72.e2**

High flow nasal oxygen (HFNO) is an emerging therapy used to treat respiratory failure. It can deliver humidified gases at a range of inspired oxygen concentrations ( $\text{FiO}_2$ ) with flows of up to 60 L/min, generating positive end expiratory pressure. In this single-centre, open-label, randomised, controlled trial, patients with cardiogenic pulmonary oedema presenting to the emergency department were randomised to either conventional oxygen therapy or HFNO in addition to standard medical therapies.

Patients aged  $\geq 18$  years were eligible if they had a clinical and radiological diagnosis of cardiogenic pulmonary oedema, oxygen saturation 90 - 94% breathing air and a respiratory rate (RR) of 25 - 35 breaths/min, despite 10 minutes of initial medical management. The need for intubation or non-invasive ventilation, myocardial infarction, cardiovascular instability, Glasgow Coma Scale score  $< 13$  and stage five chronic kidney disease all represented exclusion criteria. HFNO was commenced at 35 L/min with oxygen concentrations adjusted to achieve oxygen saturations  $\geq 95\%$ . Nasal cannula or a non-rebreather mask were used in the conventional oxygen therapy group. The primary outcome measure was the RR 60 minutes post intervention. The investigators planned to recruit 128 patients to detect a difference of 4 breaths/min between the two groups.

A total of 128 patients were included in a modified intention-to-treat analysis; 63 in the HFNO group and 65 in the conventional oxygen therapy group. A typical patient was a 70 year old female with significant co-morbidities and a baseline RR of 28. There was no difference in the baseline patient demographics, vital signs or treatments. In the HFNO group the initial  $\text{FiO}_2$  was 0.50 and median flow rate was 35 L/min. 78.5% of the conventional oxygen group received oxygen via nasal cannula at a median flow rate of 3 L/min). At 60 minutes, the mean RR was non-significantly lower in the HFNO group ( $21.8 \pm 4.1$  vs.  $25.1 \pm 3.6$  breaths/min; mean difference, 3.3; 95% CI, 1.9 to 4.6). There was no difference in intubation rates, mortality (only one patient died in the seven day follow up period) or hospital length of stay. However, the mean hospital length of stay was just 1.1 days.

### **Should we used HFNO in cardiogenic pulmonary oedema?**

Maybe, although this small trial showed no benefit in a relatively well patient cohort.

## SOS-Ventilation

**Chanques G, Conseil M, Roger C, Constantin JM, Prades A, Carr J et al. Immediate interruption of sedation compared with usual sedation care in critically ill postoperative patients (SOS-Ventilation): a randomised, parallel-group clinical. Lancet Respir Med 2017;5:795-805**

Although sedation is administered in the ICU for patient comfort and to allow tolerance of medical interventions, over-sedation is associated with prolonged ventilation, prolonged ICU length of stay and increased morbidity.<sup>1</sup> The SOS-Ventilation trial was a randomised, parallel-group, trial performed at three French ICUs, investigating whether immediate cessation of sedation after ICU admission, in comparison with usual care, improved outcomes in critically ill post-operative laparotomy patients.

Adult patients who were mechanically ventilated with a minimum of one organ dysfunction (SOFA score >1 for any organ) were eligible for recruitment. Patients were excluded if they had a brain injury, a surgical need for continued sedation, severe ARDS, treatment limitation or a history of substance abuse. A standard sedation protocol using the Richmond Agitation Sedation Scale (RASS) and the Behavioural Pain Scale (BPS), incorporating daily sedation breaks, was adopted during the trial period. The primary outcome measure was time to successful extubation.

Over two-years, 137 patients were randomised (68 to the control and 69 to the intervention). Time to successful extubation was significantly shorter in the intervention group {median 9 hrs (IQR, 4 – 40) vs. 55 hrs (IQR, 29 – 103);  $P < 0.0001$ }. This correlated with a reduction in duration of ventilation {median 8 hrs (IQR, 4 – 36) vs. 50 hrs (IQR, 29 – 93),  $P < 0.0001$ }. Furthermore, significantly fewer patients in the intervention group suffered delirium (28 vs. 48,  $P = 0.0004$ ). There was no difference in the use of noninvasive ventilation or self extubation. There was no significant difference in mortality at 28 days.

### Should we implement this into our practice?

Immediate interruption of sedation after laparotomy seems promising but requires more evidence before implementation as standard care.

1. Barr J, Fraser GL, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the ICU. Crit Care Med 2013;41:278–80.

# Gastrointestinal Trials



## TENSION

**Brunschot S, van Grinsven J, van Santvoort HC, Bakker OJ, Besselink MG, Boermeester MA et al. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. Lancet 2018;391(10115):51–58**

Acute pancreatitis is common and can be complicated by life threatening infected necrotising pancreatitis requiring surgical intervention. The introduction of a step-up approach has demonstrated that percutaneous drainage followed by minimally invasive necrosectomy may be superior to a primary open procedure. Endoscopic surgery is less invasive and may further reduce the physiological insult to an already compromised patient. The TENSION trial was a multi-centre, randomised trial comparing an endoscopic approach with a surgical step-up approach for infected necrotising pancreatitis.

Adult patients with a high suspicion or evidence of infected necrotic pancreatitis, were randomised to endoscopic or surgical management. The endoscopic group underwent endoscopic ultrasound-guided transluminal drainage and proceeded to endoscopic necrosectomy if required. The surgical group underwent radiological guided percutaneous drainage before proceeding to video-assisted retroperitoneal debridement if required. The primary endpoint was a composite of major complications or death at 6 months. Major complications were new organ failures, bleeding, visceral perforation, fistulas and hernias. Secondary endpoints included the components of the primary endpoint, pancreatic fistula, pancreatic insufficiency, biliary strictures, wound infections, need for necrosectomy, total interventions, length of hospital and ICU stay, costs and quality of life, and the numbers of crossovers.

Of the 418 patients assessed, 98 were randomised (51 endoscopic vs 47 surgical). Groups were similar at baseline, with excellent exposure to the two interventions in each group. There was no difference in the primary endpoint, 22 endoscopic patients vs 21 surgery patients (relative risk 0.97, 95% CI 0.62 to 1.51;  $P = 0.88$ ). Nor was there a mortality difference, 9 endoscopic vs 6 surgical patients (RR, 1.38; 95% CI, 0.53 to 3.59;  $P = 0.50$ ). New cardiovascular failure was less frequent in the endoscopic group (3 vs. 9 patients;  $P = 0.05$ ). There were also less pancreatic fistulas (2 vs. 13 patients;  $P = 0.001$ ) and a shorter length of stay (53 vs. 69 days;  $P = 0.01$ ) in the endoscopic group. Overall costs were not significantly different.

### **Should we routinely use an endoscopic approach for infected necrosectomy?**

Possibly. An endoscopic intervention seems promising for infected necrotising pancreatitis, although the numbers in the trial were small.

# Nutrition Trials



## Enteral Nutrition as Stress Ulcer Prophylaxis

**El-Kersh K, Jalil B, McClave S, Cavallazzi R, Guardiola J, Guilkey K et al. Enteral nutrition as stress ulcer prophylaxis in critically ill patients: A randomised controlled exploratory study. J Crit Care 2018; (43):108-113**

This exploratory double-blind, randomised controlled trial was conducted in 2 medical ICUs in the USA. The investigators hypothesised early enteral nutrition alone would be non-inferior to early enteral nutrition plus iv proton pump inhibitor in the prevention of gastrointestinal (GI) bleeding in mechanically ventilated, critically ill patients.

Adult patients expected to require  $\geq 48$  hours of mechanical ventilation and without any contraindication to enteral feeding within 24 hours were eligible for inclusion. Patients with closed head injury, burns or who had suffered a gastrointestinal bleed during hospital admission were excluded. Eligible patients were randomised using sealed, opaque envelopes, to the treatment group (enteral nutrition plus iv pantoprazole 40mg) or control group (enteral nutrition plus placebo). Study drugs were identical in appearance. The enteral nutrition formula was identical for all patients who had their calorific requirements calculated from a weight-based formula. Assessment of adequacy of enteral nutrition, in terms of gastric aspirate volumes, was protocolised.

The incidence of overt or significant GI bleeding, both clearly defined, was the primary outcome. The incidence of *C. difficile* infection was the sole secondary outcome. Of 320 patients assessed, 124 patients were randomised. 22 patients were extubated within 24 hours and thus excluded, leaving 55 patients in the treatment group and 47 patients in the placebo group. There were no significant differences in baseline characteristics, including haematological laboratory parameters, between groups. The volume of enteral feed delivered did not differ significantly between groups. Over 95% (n= 99) of patients had apparently ingested an antacid in the week prior to admission.

A median of 3 doses of study drug were delivered in each group. The incidence of overt or significant GI bleeding did not differ, 1.82% vs 2.13% (P = 0.99), in the treatment vs control groups, respectively. *C. difficile* infection occurred in 1.82% vs 6.38% in the treatment vs control groups respectively (P = 0.33). Antibiotic use within the participating units was not reported.

### **Is enteral nutrition sufficient as stress ulcer prophylaxis in mechanically ventilated patients ?**

As a small exploratory study, this should not change practice. Larger studies are in progress.

## SPIRIT

**Jakob M, Bütikofer L, Berger D, Coslovsky & Takala J. A randomized controlled pilot study to evaluate the effect of an enteral formulation designed to improve gastrointestinal tolerance in the critically ill patient—the SPIRIT trial. *Critical Care* 2017;21:140**

Diarrhoea in the critically ill is common, discomforting, increases nursing workload and may predispose to decubitus ulceration and difficulty absorbing enteral nutrition. SPIRIT aimed to evaluate whether a novel enteral formula (Peptamen® AF, a high calorie-density, high-protein feed containing hydrolysed whey protein (35% of calories), medium chain triglycerides and fish oils) could alleviate diarrhoea and other gastrointestinal symptoms in the critically ill.

This was a pilot, prospective, double-blind, single-centre, randomised controlled study conducted in a Swiss ICU. Eligible adults were ≥18 years old with an expected ICU stay of ≥5days. Those already receiving (or with a contraindication to) enteral nutrition were excluded. 90 patients were randomised over 16 months from January 2013 to August 2014 to feeding with Peptamen® AF or the control feed Isosource® Energy (16% calories from non-whey protein). Tube feeding was instituted up to 72 hours following ICU admission, to a target of 25kcal/kg/day, adjusted to caloric estimates by indirect calorimetry thereafter. Study feed was given for up to 10 days, faecal management systems were at the bedside nurse's discretion. No sample size calculation was performed as this was an exploratory pilot study.

Baseline median (IQR) values for age (63 (51-73) years) and SAPS II (61.0 (47.8–74)) were similar between groups. Nine patients at entry had diarrhoea, residual gastric volume was 35 / 50 mls in the intervention / control groups respectively (NS). Patients reached their caloric goals after 2.2 (0.8-3.7) days and 2.0 (1.3-2.7) days in the intervention / control groups respectively (P=0.16). In the intervention / control group diarrhoea occurred in 64% vs 70% (P=0.65) requiring a faecal management system in 51% vs 55% (P=0.83) respectively. There were no differences seen in calorie intake, nursing workload or exploratory clinical outcomes. Patients receiving Peptamen® AF unsurprisingly received more protein.

### **Should we rush to change our default enteral nutrition?**

No. Both enteral products were associated with a high incidence of diarrhoea. The high protein content of the Peptamen® AF feed is an area of current interest. Future research should take note of its tolerability as well as any effect on clinical outcomes.

## EAT-ICU

**Allingstrup MJ, Kondrup J, Wiis J, Claudius C, Pedersen UG, Hein-Rasmussen R. Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial. *Intensive Care Med* 2017;43(11):1637-1647**

Nutritional support in the ICU was always driven by the presumption that patients needed to be fed, and the more catabolic they were the greater their nutritional requirement. However, over the past decade evidence has emerged for harm resulting from early feeding, possibly due to an inhibition of autophagy, a housekeeping process of clearing cellular debris during times of stress.

EAT-ICU was a single centre, assessor-blinded randomised trial comparing early goal-directed nutrition (EGDN) with standard care in critically ill patients. Eligible patients were adults with an expected ICU length of stay  $\geq 3$  days, receiving mechanical ventilation, and with a central venous catheter. A nutritional risk assessment was not undertaken, although visibly malnourished and those with a BMI  $\leq 17$  were excluded. 100% of calorific requirement was administered, enteral and parenterally, in the EGDN group, guided by indirect calorimetry and urinary nitrogen testing. The standard group were fed enterally at the recommended dose of 25 kcal/kg/day. Blood glucose was maintained at between 6 and 10 mmol/L. Residual gastric volume was monitored and managed with reduction of feed volume and/or the use of prokinetics. 200 patients were required to demonstrate a 15% relative reduction in the primary outcome of physical component summary score of the Medical Outcomes Study 36-item short form health survey version 2, with 80% power at a 5% significance level.

203 patients were randomised, with groups being relatively equal at baseline. There was good exposure to the allocated feeding regimes. The median calculated energy requirement did not differ between the groups. The EGDN group received more energy (97% energy goals vs. 64%) and protein (97% vs. 45%) than the standard care group. There was no difference in the primary outcome (EGDN group, 37% vs. standard care group, 35%). Despite receiving significantly more energy and protein over the course of their ICU stay, there were no differences in any secondary outcomes, including mortality, length of ICU or hospital stay, organ support requirement or nosocomial infection rates.

**Should we feed our patients using an early goal-directed approach based on indirect calorimetry and urinary nitrogen testing?**

No. This small trial does not provide evidence of benefit from a more labour intensive and expensive form of nutrition.



# Renal Trials



## HYDRAREA STUDY

**Valette X, Desmeulles I, Savary B, Masson R, Seguin A, Sauneuf B et al. Sodium Bicarbonate Versus Sodium Chloride for Preventing Contrast-Associated Acute Kidney Injury in Critically Ill Patients: A Randomized Controlled Trial. Crit Care Med 2017;45(4):637-644**

Guidelines to prevent contrast-associated acute kidney injury (CA-AKI) in ICU patients advocate intravascular volume expansion with isotonic sodium chloride (NaCl) or sodium bicarbonate (NaHCO<sub>3</sub>). The HYDRAREA trial investigated the use of these fluids in 3 French ICUs. Eligible patients were adults with an expected ICU length of stay > 48 hrs receiving intravenous contrast for planned imaging. Patients with anuria or rising serum creatinine in the previous 48 hours, receiving renal replacement therapy (RRT), pregnancy, expected non-survival or potential contra-indication to volume or bicarbonate loading were excluded.

The study was powered ( $\alpha$  0.05,  $\beta$  0.2) based on an expected 10% absolute reduction in the rate of CA-AKI with NaHCO<sub>3</sub> vs. NaCl (5% vs. 15%). 320 of 1,458 screened patients were randomised to receive either 3 ml/kg of 0.9% NaCl (n = 162) or 1.4% NaHCO<sub>3</sub> (n = 158). The modified intention-to-treat analysis excluded 13 patients (2 did not receive contrast, 11 were included incorrectly). Groups were well matched at baseline; a typical patient was a 55 years old male with a medical or emergency surgery reason for admission. 81% were mechanically ventilated, 33% received catecholamines and 35% were septic. Baseline median renal indices were normal. Patients received a median (IQR) of 90 (70 - 105) mls of low-osmolar contrast medium prior to CT (63%) or angiography (37%).

The primary endpoint of new CA-AKI was defined as either an increase in serum creatinine {by 0.3 mg/dl (27  $\mu$ mol/l) or by  $\geq$  50% from baseline} or by 6 hours of oliguria ( $\leq$  0.5 ml/kg/hr) within 72 hours of contrast exposure. There was no difference between the groups for this outcome (33% NaCl vs. 35% NaHCO<sub>3</sub>; adjusted relative risk, -1.8%; 95% CI, -12.3 to 8.9; P = 0.81), nor when using alternative CA-AKI criteria, nor in secondary endpoints (use of RRT, ICU length of stay & mortality.) NaHCO<sub>3</sub> increased mean urinary pH compared to NaCl (6.7 vs. 6.2, P <0.0001).

### **Should we use NaHCO<sub>3</sub> in preference to NaCl to prevent CA-AKI?**

No. There was no benefit seen in this study. The use of NaCl itself for this purpose is largely extrapolated from use in non-ICU populations. Its true effectiveness remains unclear.

## AMACING

### **Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy: a prospective randomised, phase 3, controlled, open-label, non-inferiority trial. *The Lancet* 2017;389(10076):1312-1322**

Guidelines, based on expert consensus opinion, recommend the administration of isotonic sodium chloride (NaCl) peri-procedurally in patients at high risk of developing contrast-induced nephropathy. The clinical risk and financial cost associated with prophylactic administration of IV fluids to this group may be significant, given up to 12 million high risk patients may be exposed to contrast annually.

This single-centred, open-label, randomised, controlled trial aimed to compare prophylactic hydration with no prophylaxis in a high risk patient group. Patients were included if they had an estimated glomerular filtration rate (eGFR) of 45 – 59 ml/min/1.73m<sup>2</sup> and diabetes or at least two other risk factors. Those with an eGFR 30 – 45 ml/min/1.73m<sup>2</sup>, multiple myeloma and those with lymphoma and light chain proteinuria were also eligible for inclusion. Over 90% of study participants had the procedure performed as an out-patient. Emergency admissions and intensive care patients were excluded from this trial.

Clinical staff and patients were unblinded to treatment group allocation. Both groups were well matched at baseline in terms of risk factors and volume of administered contrast. The prophylactic hydration group (n = 328) received a mean of 1,637 ml (SD 950) of NaCl. The control group (n = 332) received no prophylactic hydration.

The primary end-point was the incidence of contrast-induced nephropathy in each group. Contrast-induced nephropathy was defined as an increase in serum creatinine by more than 44 µmol/L or 25% within 2 – 6 days of exposure. Data for day 2 – 6 creatinine was available for 91% of participants (n = 603). There was no difference in the primary outcome, 2.7% (n=8) vs. 2.6% (n=8) in the hydrated vs. non-hydrated groups, respectively (absolute difference, -0.1%; one sided 95% CI, -2.25 to 2.06; one-tailed P = 0.47). No prophylaxis was associated with significant cost savings (mean difference, -\$663; 95% CI, -\$1,234 to -\$191). 5.5% (n = 18) of patients in the hydrated group suffered some complication.

#### **Should we avoid pre-hydration with IV fluids for the prevention of contrast-induced nephropathy in the critically ill?**

No. The results of this trial should not be applied in isolation to a critically ill population.

## LICRA

**McIlroy D, Murphy D, Kasza J, Bhatia D, Wutzlhofer, Marasco S. Effects of restricting perioperative use of intravenous chloride on kidney injury in patients undergoing cardiac surgery: the LICRA pragmatic controlled clinical trial. *Intensive Care Med* 2017;43:795-806**

With the effective withdrawal from use in ICUs of synthetic colloid solutions, attention has shifted to the potential harmful effects of chloride loading from unbalanced crystalloids. Rational concerns about the renal effects of hyperchloraemia have yet to be translated into firm evidence of adverse clinical outcomes.<sup>1</sup>

LICRA was an Australian pragmatic, prospective, open-label study where the default peri- and post-operative fluid for strata of patients undergoing cardiac surgery changed from chloride-rich (0.9% sodium chloride, 4% albumin) to chloride-limited (Hartmann's then Plasmalyte-148, 20% albumin) to chloride-rich again in sequential 5-month blocks. Bypass circuits were primed with Hartmann's throughout and clinician-ordered non-protocol fluids were allowed. The planned study size of 1,000 patients was calculated to have > 90% and 70% power, respectively, to detect the hypothesised 33% / 40% reduction in the co-primary endpoints of peak change in serum creatinine ( $\Delta$ SCr) and stage 2 or 3 acute kidney injury {AKI, Kidney Disease: Improving Global Outcomes (KDIGO) criteria} within 5 days. Patients were enrolled sequentially prior to consent (with ethical approval) and given the option to opt-out of later data analysis.

1,298 patients were enrolled and 162 were excluded (142 had surgery during pre-specified transition periods). Mean age was 63, 71% were male and 40% elective. Perioperative risk (Euroscore) did not vary between groups, but those in the chloride-rich strategy had a 9% lower estimated glomerular filtration rate. There was high (> 95%) adherence to the assigned fluid strategy and those in the chloride-rich strata had a significantly greater chloride load (median 210 vs. 173 mmol), leading to more hyperchloraemia ( $S_{Cl^-} > 110$  mmol/l; 93.5% vs. 66.3%;  $P < 0.001$ ) and more acidaemia ( $pH < 7.3$ ; 63.8% vs. 42.3%;  $P < 0.001$ ). There was no difference in either primary outcome (median peak  $\Delta$ SCr, 13 vs. 13  $\mu$ mol/l;  $P = 0.32$ ; stage 2/3 AKI, 10.8% vs. 10.5%; RR, 1.03; 95% CI, 0.71 to 1.50;  $P = 0.88$ ). Secondary outcomes were also unaffected.

### **Should cardiac ICUs abandon 0.9% Saline in favour of Hartmann's Solution?**

No. In the setting of no outcome benefit (or harm) clinicians can weigh up the benefits of reduced costs against the elegance of avoiding unnecessary acidosis.

1. Young P, Bailey M, Beasley R, et al. Effect of a Buffered Crystalloid Solution vs. Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT RCT. *JAMA* 2015;314(16):1701–10.

## Spironolactone in Cardiac Surgery AKI

**Barba-Navarro R, Tapia-Silva M, Garza-Garcia C, Lopez-Giacoman S, Melgoza-Toral I, Vazquez-Rangel A et al. The Effect of Spironolactone on Acute Kidney Injury After Cardiac Surgery: A Randomised Placebo-Controlled Trial. Am J Kidney Disease 2017;69(2):192-199**

This single centre, double-blind, randomised controlled trial in a Mexican cardiac surgical unit, hypothesised spironolactone would reduce the incidence of acute kidney injury (AKI) in cardiac surgical patients. Those undergoing cardiac surgery were randomised to receive 100 mg of spironolactone 12-24 hours pre-operatively and then given a further 25 mg on days 0,1 and 2. The control group received placebo.

The primary outcome was the development of AKI, as defined by Kidney Disease: Improving Global Outcomes (KIDGO) criteria. Secondary outcomes included the requirement for renal replacement therapy, length of ICU stay and mortality. Patients with pre-existing chronic kidney disease (defined as creatinine > 141 mmol/L) were excluded from the study.

141 patients were required in each group to detect a between-group difference of 15% in the incidence of AKI, with 80% power at a 5% significance level. After exclusion criteria, low enrolment rate and funding issues, together with loss to follow-up, only 115 and 118 patients were included in the final analysis of the treatment and control groups, respectively. Compliance with assigned dosing schedules was 100% in each group.

98% (n = 228) of recruited cases were elective. The treatment group had a higher incidence of diabetes at baseline 31% (n = 36) vs. 21% (n = 18) (P = 0.02). 65% (n = 151) of patients underwent valvular surgery only. Cardiopulmonary bypass time, intra-operative blood pressure, aortic cross clamp time, intra-operative fluid replacement and blood loss did not differ significantly between groups.

The incidence of AKI was higher in the treatment group, 43% (n = 50) vs. 29% (n = 34) (P = 0.02). No difference in secondary outcomes was observed. The increase in AKI was predominantly at stage 1; 35.6% vs. 22% in the treatment vs. control groups, respectively. Only 3% (n = 8) of patients required renal replacement therapy.

### **Should we implement this into our practice?**

No. This study does not support the use of spironolactone to reduce the incidence of post-operative AKI in cardiac surgical patients. The results indicate a potential signal of harm from this intervention.

# Endocrine Trials



## HALF PINT

### **Agus MS, Wypij D, Hirshberg EL, Srinivasan V, Faustino EV, Luckett PM et al. Tight Glycemic Control in Critically Ill Children. N Engl J Med 2017;376:729-41**

Although tight glycaemic control does not improve outcomes in critically ill adults, evidence in children outside of cardiac surgery is limited. The Heart and Lung Failure–Paediatric Insulin Titration (HALF-PINT) trial was a 35 centre unblinded, randomised control trial comparing tight glycaemic control (4.4 to 6.1 mmol/L) with a more liberal glycaemic target (8.3 to 10.0 mmol/L) in critically ill children with hyperglycaemia who had cardiovascular or respiratory failure. The investigators hypothesised that tight glycaemic control would improve outcomes.

Children aged 2 weeks to 17 years who were receiving vasopressors or required mechanical ventilation and had two blood glucose measurements greater than 8.3 mmol/L were eligible. Diabetic or post cardiac surgery children were excluded. The blood glucose level was controlled with a continuous IV insulin guided by the bedside computerised Children’s Hospital Euglycemia for Kids Spreadsheet (CHECKS). The primary outcome was the number of ICU-free days at 28 days. Secondary outcomes included 90-day mortality, organ dysfunction, ventilator-free days to day 28, the incidence of healthcare-associated infection and hypoglycemia.

The study was stopped early due to futility after recruitment of 713 patients, with 360 patients randomised to the tight control group and 353 patients to the liberal group. There was a significant separation in the median time-weighted average glucose levels {lower target group, 6.1 mmol/L (IQR, 5.7 - 6.6) vs. 6.8 mmol/L (IQR, 6.0 – 7.9), in the higher-target group,  $P < 0.001$ }. The majority (98.6%) of the lower target group received insulin versus 61.6% in the liberal group. Hypoglycaemia occurred more frequently in the lower-target group (3.7% vs. 0.3%;  $P = 0.01$ ). In the intention-to-treat analysis, the median number of ICU-free days did not differ significantly between the lower-target group and the higher-target group, 19.4 days (IQR, 0 - 24.2) vs. 19.4 days (IQR, 6.7 - 23.9),  $P = 0.58$ . Patients in the lower-target group also had higher rates of healthcare-associated infections (3.4% vs. 1.1%,  $P = 0.04$ ). No significant differences were observed in mortality, severity of organ dysfunction, or the number of ventilator-free days.

#### **Should we routinely target tight glycaemic control in nondiabetic children?**

No. There is no benefit, and possible harm, with tight glycaemic control in critically ill children.

# Haematology Trials





### TRICS III

**Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, et al. Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery. N Engl J Med 2017; 377:2133-2144**

Several randomised controlled trials over the past 2 decades have reported similar outcomes whether a restrictive or liberal red cell transfusion threshold is used. However, there is ongoing concern regarding the presence of active cardiac ischaemia, and whether this group of patients should have a higher threshold for transfusion than other patients. A recent randomised controlled trial (TITRe2) in the cardiac surgery setting suggested worse outcomes with a restrictive transfusion strategy, which was at odds with the majority of the evidence-base.

TRICS III was an international, multi-centre, open-label, non-inferiority, randomised controlled trial, comparing a restrictive transfusion threshold of 75 g/L with a liberal one of 95 g/L, in patients undergoing cardiac surgery. The liberal threshold dropping to 85 g/L on the ward. Eligible patients were due to undergo cardiac surgery requiring cardiopulmonary bypass and had a moderate-to-high risk of death as determined by their EuroSCORE I. Those unable or unwilling to receive blood, or undergoing heart transplantation or ventricular assist device insertion, were excluded. The transfusion strategy ran from the commencement of anaesthesia to hospital discharge or day-28. One unit of red cells was transfused at a time. 5,000 patients were required to detect a 3% noninferiority margin ( $\beta$ , 0.85; one sided  $\alpha$ , 0.025), assuming a baseline rate of 10% of the primary composite outcome including death, myocardial infarction and stroke.

5,243 patients were randomised from 73 centres in 19 countries, with 5,092 included in a modified intention-to-treat analysis. The groups separated well, with 10 g/L difference in haemoglobin concentrations. The liberal transfusion group received more transfusions (72.6% vs. 52.3%;  $P < 0.001$ ). There was no difference in the primary outcome (restrictive strategy, 11.4% vs. liberal strategy, 12.5%; absolute risk difference, -1.11%; 95% CI, -2.93 to 0.72; OR 0.90; 95% CI, 0.76 to 1.07). There were no significant differences in any other outcomes.

#### **Should cardiac surgery patients receive a restrictive transfusion strategy?**

Yes. The result of TRICS III is consistent with the majority of the evidence-base for transfusion thresholds, including those in the critically ill.

## TRIBE

**Palmieri T, Holmes J, Arnolde B, Peck M, Potenza B, Cochran A et al. Transfusion Requirement in Burn Care Evaluation – A Multicentre Randomised Prospective Trial of Blood Transfusion in Major Burn Injury. Ann Surg 2017;266(4):595-602**

The American multi-centre, randomised controlled TRIBE trial examined whether a restrictive transfusion policy would reduce bloodstream infection (BSI), organ dysfunction and mortality in critically ill burns patients, within 96 hours of injury and suffering  $\geq 20\%$  total body surface area burns (TBSA). The anticipated requirement for surgical burn excision and grafting was also a stipulation of inclusion. Patients with chronic anaemia, a Glasgow Coma Scale score  $< 9$ , angina, acute myocardial infarction and dialysis prior to admission were excluded.

Patients were randomised to either a restrictive (target haemoglobin, Hb, 70 – 80 g/L) or a liberal transfusion strategy (target Hb 100 – 110 g/L) for the duration of their hospital admission. An adaptive random allocation procedure ensured treatment groups were balanced between sites with respect to age & TBSA of burn. Packed red cells were transfused, one unit at a time, in the restrictive group when the Hb  $< 70$  g/L and in the liberal group when Hb  $< 100$  g/L. Analysis was by intention-to-treat. It was estimated 345 patients were required at 80% power and a 1 sided  $\alpha$ -level of 0.05 to identify (an unclear) difference in rates of BSI, mortality and other secondary endpoints.

Of 14,817 patients assessed for eligibility, 347 were recruited (1,77 to the liberal group and 1,70 to the restrictive group). Two patients allocated to the restrictive group did not meet inclusion criteria. 80% (n = 273) of recruited patient were male with a mean age of 41 years in each group. Groups were well balanced at baseline with respect to % TBSA, thickness of burn and presence of inhalational injury. Compliance with the transfusion protocol was 90.6% vs 88.0% in the liberal vs restrictive groups, respectively. The restrictive group received a significantly fewer number of red cell units/patient, 7 (2 - 19) vs 15 (7 - 31);  $P < 0.001$ . A greater proportion of patients in the restrictive group received no transfusion at all (16.1% vs. 6.8%,  $P = 0.011$ ).

No significant differences were seen in the primary outcome of BSI {23.7% (n = 42) vs. 23.8% (n = 40)} in the liberal vs. restrictive groups, respectively, or 30-day mortality, wound infection, wound healing, MOD score, ICU or hospital length of stay.

### **Should we use a restrictive transfusion strategy in burns patients?**

Probably. This is consistent with the evidence-base for transfusion in the critically ill.

# Sepsis Trials



## PRISM

### **The PRISM Investigators. Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis. *N Engl J Med* 2017;376:2223-2234**

The Rivers early goal-directed therapy sepsis trial of 2001 proved controversial, and led to three further randomised controlled trials, providing further data on an international basis. The American ProCESS trial, the Australian & New Zealand ARISE trial and the British ProMISe trial, all sought to replicate the findings of the original RIVERS trial, aiming to increase oxygen delivery and, if necessary, decrease oxygen consumption. To improve statistical power and explore heterogeneity of treatment effect from these trials, an individual patient-level meta analysis was undertaken, combining the data from these three trials.

The trials were harmonised prior to their commencement, allowing pooling of all data on an individual-level, with the exception of the standard therapy group from the ProCESS trial, as this group was not replicated in the other two trials. 3,723 patients from 138 hospitals in 7 countries were included. Groups were similar at baseline and separated well with exposure to their respective strategies.

There was no difference in the primary outcome of 90-day mortality between early goal-directed therapy (24.9%) and usual care (25.4%); adjusted odds ratio, 0.97; 95% CI, 0.82 to 1.14;  $P = 0.68$ . Early goal-directed therapy was, however, associated with a greater use of intensive care (mean  $\pm$  SD;  $5.3 \pm 7.1$  vs.  $4.9 \pm 7.0$  days;  $P = 0.04$ ), cardiovascular support ( $1.9 \pm 3.7$  vs.  $1.6 \pm 2.9$  days,  $P = 0.01$ ) and resulted in higher average costs than with EGDT. There was no evidence of benefit with early goal-directed therapy in those with the most severe septic shock, the top tercile of APACHE II scores and those in the top tercile of predicted risk of death.

Despite PRISM showing no benefit from the use of early goal-directed therapy, aspects of the Rivers early goal-directed therapy protocol, such as early fluids, have become ingrained as part of usual care. However, most components of this package of care has now been deemed obsolete, including resuscitating against a central venous pressure and targeting a haemoglobin concentration of 100 g/L.

#### **Should early-goaled directed therapy in sepsis be used?**

No, not as originally described. Three more modern studies convincingly show no benefit to this more resource-intensive approach, a finding confirmed with meta analysis.

## Pseudomas Vaccine

**Rello J, Krenn CG, Locker G, Pilger E, Madl C, Balica L et al. A randomised placebo-controlled phase II study of a Pseudomonas vaccine in ventilated ICU patients. Critical Care 2017;21:22**

This phase II, multi-centre, randomised controlled trial aimed to assess the optimal dose, safety profile and immunogenicity of IC43, a novel protein-based vaccine against *Pseudomonas aeruginosa*.

IC43 is based on recombination of two epitopes of the outer membrane proteins, OprF and OprI, which are conserved across all serotypes of *P. aeruginosa*. The trial was funded by Valneva, the company which developed the vaccine and for whom two of the lead investigators of the study are employed.

All mechanically ventilated, adult patients admitted to the ICU and expected to remain intubated for more than 48 hours were eligible for inclusion. Those with a low severity of illness (acute physiology score < 8), coagulopathy or thrombocytopenia, were among those excluded. The primary outcome measure was the immunogenicity of IC43 at day 14, as defined by the OprF/I-specific IgG antibody titre.

Of 408 patients assessed, 401 mechanically ventilated patients were randomised as soon as possible after admission to ICU to one of 4 groups – IC43 100 µg with adjuvant, IC43 100 µg without adjuvant, IC43 200 µg with adjuvant or placebo. As the IC43 100 µg without adjuvant preparation differed in appearance to the other three, staff could not be blinded to this preparation. Patients received an intramuscular dose of IC43 on day 0 and a second dose at day 7 if possible. Follow-up was for 90 days. Analysis was by intention-to-treat.

77.6% (n = 311) of patients recruited were medical admissions, with 66.6% (n=374) male and a mean age of 56.1 years. Significantly higher titres of IgG antibodies were detected in all treatment groups compared with placebo (P < 0.0001). Future trials of IC43 will dose using 100 µg without adjuvant, as seroconversion was highest with this preparation (80.6%). There was no significant difference in serious adverse events between groups (P > 0.05) and < 5% of patients suffered local tolerability symptoms.

### **Should we implement this into our practice?**

No. This was a phase II study and we must await further trials of IC43 to clarify any potential role it may play in the prevention of *Pseudomonas aeruginosa* infection.

## Low Dose Hydrocortisone in Sepsis

**Qing-quan L, Xiao-hua G, Qi-hong C, Jiang-quan Y, Rui-qiang Z. Early initiation of low dose hydrocortisone treatment for septic shock in adults: A randomised clinical trial. Am J Emerg Med 2017;35(12):1810-1814**

This double-blind, placebo-controlled, randomised clinical trial was conducted at a 35 bedded, university affiliated ICU in China, from September 2015 to September 2016. The trialists hypothesised early administration of hydrocortisone therapy, simultaneous to the commencement of vasopressor treatment, would reduce 28-day mortality (primary outcome) in patients who had been diagnosed with septic shock. The power calculation used an estimated 60% control group mortality. We are not told of the effect size on 28 day mortality the hydrocortisone was estimated to have.

120 patients admitted to the ICU within 6 hours of a diagnosis of septic shock were randomised to receive a 200 mg/day hydrocortisone infusion or placebo. Randomisation was by computer generated random numbers. Patients who were immunosuppressed, were receiving, or had received, steroid within 3 months were excluded.

Septic shock was defined as sepsis-induced hypotension with a systolic blood pressure (SBP) of < 90 mm Hg or a drop in SBP of > 40 mm Hg from baseline, despite adequate fluid resuscitation. Goal directed therapy was initiated; 1.0 – 1.5L of crystalloid was administered to target a central venous pressure of 8 - 12 mm Hg; packed red cells ± dobutamine were used to target a ScvO<sub>2</sub> ≥ 70%. Noradrenaline was the vasopressor of choice (target MAP ≥ 65mmHg). Hydrocortisone or placebo was administered via continuous infusion for 6 days. If patients remained haemodynamically stable for 24 hours after cessation of vasopressor, protocolised tapering of the infusion was commenced.

118 patients were analysed by the intention-to-treat principle, (intervention, n = 58 and control, n = 60). There were important between-group differences at baseline e.g. mean APACHE II score of 25.5 ± 9.5 vs. 21.3 ± 6.9 (P=0.007), respectively. Abdominal cavity infection was lower in the treatment group, 36.2% vs. 56.7%, P = 0.026. The volume of IV fluid administered in the treatment group prior to initiation of vasopressor was also significantly lower, 1.0L (IQR, 0.7 – 1.6) vs. 1.5L (IQR, 1.0 – 2.98), P = 0.013. 28-day mortality was 39.7% vs. 31.7%, (P = 0.365), in treatment vs. control groups, respectively. There was no difference in hospital mortality, ICU or hospital length of stay.

### **Should we implement this into our practice?**

No. This trial was underpowered to answer the question.

# Miscellaneous Trials



## ICATIBANT

**Sinert R, Levy P, Bernstein J, Body R, Sivilotti M, Moellman J et al. Randomised Trial of Icatibant for Angiotensin-Converting Enzyme Inhibitor-Induced Airway Angioedema. *J Allergy Clin Immunol Pract* 2017;5(5):1402-1409**

Icatibant is a selective bradykinin B2 receptor antagonist which has been approved for the treatment of hereditary angioedema. This randomised, double-blind, placebo-controlled trial recruited patients from the emergency departments of 31 centres in 4 different countries.

The investigators hypothesised icatibant would reduce time-to-meeting discharge criteria in patients admitted with ACE-inhibitor (ACE-I)-induced angioedema. Adult patients presenting within 12 hours of symptom onset, with at least moderately severe angioedema, were eligible. Patients requiring intubation were excluded as were those with known hereditary, allergic or known acquired angioedema. Patients were randomised in a 1:1 ratio to receive a single dose of icatibant (30 mg) subcutaneously or placebo. The randomisation process was stratified by symptom severity and race. The primary endpoint was the time taken to meet discharge criteria, defined as the absence of difficulty breathing and difficulty swallowing, together with mild or absent tongue swelling and voice change. The study was funded and sponsored by Shire HGT who also conducted the statistical analysis.

One hundred and twenty one patients were randomised, with 61 vs. 60 patients in the treatment vs. control groups, respectively. A total of 55% (n = 66) of recruited patients were admitted to hospital with 25% (n = 30) admitted to ICU, but only one patient subsequently required intubation. 69.4% (n = 89) of patients were Black or African-American and lisinopril was the most common ACE-I associated with presentation (69.4%, n = 89). 90.9% (n = 110) of patients had received one or more conventional medications prior to study drug administration (antihistamine, corticosteroid or adrenaline). Three patients did not receive the allocated study treatment. Injection site reactions were more common in the icatibant group, 65% vs. 31%. The median time to treatment was 7.8 hours (IQR 5.5 to 9.6) from symptom onset in both groups. There was no difference in the primary outcome of time-to-meeting discharge criteria (median 4 hours in each group, P = 0.63).

### **Should we implement this into our practice?**

No. Icatibant was not superior to placebo in the treatment of ACE-I induced angioedema in this trial.



# **Section 3: The Best Open Access Critical Care Guidelines of 2017**



# Neuromuscular Guidelines

## Delirium

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## **The Authors**

### **Dr Chris Gowers**

Chris Gowers is a Consultant in ICM and Anaesthesia in the Ulster Hospital, Belfast. He qualified from Nottingham University in 1997 and trained in England, Australia and Northern Ireland. He is currently the hospital's FICM tutor and has interests in teaching, cycling and end-of-life care.



### **Dr Dominic Trainor**

After completing an intercalated degree in Medical Genetics, Dominic graduated with honours from Queen's University Belfast in 2002. He undertook a Fellowship at The Alfred Hospital, Melbourne from 2013-2014. His special interests include end-of-life care and focused intensive care echocardiography. He is currently clinical lead for organ donation in The Royal Victoria Hospital, Belfast.



### **Dr Peter McGuigan**

Peter McGuigan is a consultant in ICM & anaesthesia in the Royal Victoria Hospital, Belfast. He attended Queen's University Belfast and trained in Northern Ireland. He subsequently undertook a fellowship in the Royal Melbourne Hospital, Australia where he developed an interest in clinical governance. His main clinical interests are in post cardiac arrest care and anaesthesia for head and neck surgery.



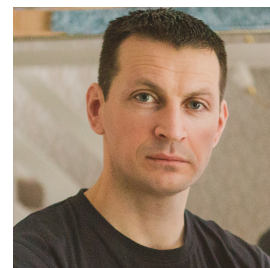
### **Dr Chris Nutt**

Chris is an intensivist & anaesthetist in the Royal Victoria Hospital, Belfast. He graduated from Queen's University Belfast in 2001 and began training in Anaesthesia and Intensive Care in 2003. He has a strong research interest, publishing on preoperative risk assessment & has collaborated on several major international trials.



### **Dr Rob Mac Sweeney**

Rob is an intensivist in the Regional Intensive Care Unit at the Royal Victoria Hospital, Belfast. He attended medical school at University College Dublin, undertook a PhD at Queen's University Belfast and completed his anaesthetic and ICM training in Northern Ireland. He started Critical Care Reviews in 2009.



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Written by

Chris Gowers | Chris Nutt | Dominic Trainor | Peter McGuigan | Rob Mac Sweeney