Critical Care Reviews Meeting 2016

Titanic Centre, Belfast


Critical Care
Reviews

Dedicated to our friend and colleague, John Hinds

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CCR Welcome

Welcome to the 4th annual Critical Care Reviews Meeting, discussing the the biggest studies of 2015 with their chief investigators and other eminent intensivists. I'm delighted to be able able to say we have chief investigators or co-investigators for four of the five biggest critical care studies by Altimetric score from the past year.

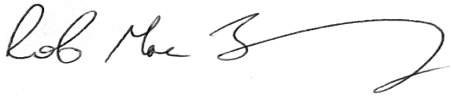
I would particularly like to welcome our faculty, who have travelled from across the world to join us, and our growing number of delegates, who have come from throughout Ireland, North and South, the UK, Europe and even as far away as the USA.

When I started the Critical Care Reviews website in 2009, I did so out of an interest in the science that underpins our speciality, and the research that informs this scientific basis. Over the past seven years, Critical Care Reviews has grown from a website into a project spanning a website, a weekly newsletter, an international meeting, and an affiliated journal. This project continues to grow, with this meeting booklet acting as a forerunner for a separate annual book, critiquing the major research of the year. Two friends, Peter McGuigan and Chris Nutt, have worked tirelessly over the past several weeks to compile these reviews. In addition, a new Critical Care Reviews podcast will start in the next few weeks, discussing present and future critical care trials.

This Meeting has been supported by our numerous loyal sponsors, including our Gold Sponsor Dräger, our silver sponsors Cardiac Services and Nikkiso, and our Bronze sponsors Vygon and Gilead Sciences. The SMACC Charity C4 have also gifted an unrestricted grant and other financial assistance.

I hope you enjoy today as much as I will. Thank you all for coming, from near and far.

With best wishes



Rob Mac Sweeney

Critical Care Reviews

NIICS
The Northern Ireland Intensive Care Society

NIICS Welcome

The Northern Ireland Intensive Care Society is pleased to join with Critical Care Reviews for the Critical Care Reviews Meeting 2016. This year sees Critical Care Reviews build on the success of the previous three years, moving to a larger venue in Belfast, and attracting a wider audience.

The wealth of talent presenting at the meeting will surely bring the most current and topical evidence, ideas and practices to the Northern Ireland Critical Care community, and allows us direct access to those advancing critical care practice throughout the world. The NIICS continues its role to support the training and education of its members and this year plans to continue the Coppel Prize Meeting , which will be held again this coming spring. We continue to represent the interests of Northern Ireland on the UK Critical Care Leadership Forum, and have a seat on the Council of the Intensive Care Society of Ireland.

To be successful, our Society relies on an active and engaged membership, and we would invite you all to join us and help build a strong voice and enthusiastic body. We seek involvement from interested members across our local critical care teams, and aim to have our inaugural North West Autumn meeting in Derry later this year, coordinated by Dr Noel Hemmings. Critical care is a team effort, and we will focus on developing our activities across all our membership groups. We need your ideas, expertise and drive. Please visit our website at www.niics.com.

Yours sincerely

John McCaffrey
President, Northern Ireland Intensive Care Society

PROGRAMME

Session 1

Chairs: Dr Anna Batchelor & Dr Rosalind O'Reilly

09:00	Rob Mac Sweeney	Welcome
09:05	The Great Debate: RCTs are Killing Critical Care	
	Jean-Louis Vincent	Damn Right!
	Luciano Gattinoni	You're Having a Laugh?
09:45	Paul Young	Saline or Plasmalyte? Is SPLiT the Solution?
10:10	John Holcomb	How to Resuscitate PROPPERly
10:35	Tim Walsh	Is Old the New Young? The ABLE Trial
11:00	Coffee	

Session 2

Chairs: Dr John McCaffrey & Dr Michelle Fallon

How I Manage...

11:30	Luciano Gattinoni	Hypoxaemic Respiratory Failure
11:45	Jean-Louis Vincent	Septic Shock
12:00	Paul Young	Pyrexia in ICU-acquired
12:15	John Holcomb	Traumatic Haemorrhage
12:30	Tim Walsh	Anaemia in ICU
12:45	Audience Questions	You do WHAT !!!
13:00	Lunch	

Session 3

Chairs: Dr Ganesh Suntharalingam & Dr Marianne Fitzgerald

14:00	Paul Young	Should we treat the HEAT
14:25	Anthony Gordon	Vasopressin or Noradrenaline: Should either Vanish?
14:50	Tim Walsh	Does Rehab help ICU patients RECOVER?
15:15	Rob Mac Sweeney	2015 Critical Care Literature: The Best of the Rest
15:40	Coffee	

Critical Care Reviews

PROGRAMME

Session 4

Chair: Rob Mac Sweeney

16:10 Panel Discussion 2015 Critical Care Literature: What I Thought of It
16:35 John Hinds Trauma Lecture
Brian Burns Trauma Care – Back to the Future
17:15 Buffet

The Fifth Session

18:00 An Informal Chat With

John Holcomb | Tim Walsh | Jean-Louis Vincent | Danny McAuley
Anthony Gordon | Paul Young | Brian Burns | You

Meeting End

19:00 *Pre-Dinner Talk*
Chris Andrews My Great Great Uncle Mr Thomas Andrews:
The Man Who Built Titanic

19:30 Dinner

Speakers

Luciano Gattinoni

Luciano Gattinoni is Professor in Anesthesiology and Intensive Care Medicine, University of Milan; Department of Pathophysiology and Transplantation, University of Milan; and Chief of the Department of Anesthesia, Intensive Care and Emergency, Policlinico Hospital of Milan.

After obtaining board certifications in Anesthesiology, Critical Care Medicine and Laboratory Medicine, between 1976 and 1980 he was appointed as a Visiting Fellow and Visiting Professor at the National Institutes of Health (USA). In the early 1980's, he introduced the concept of lung rest by extracorporeal CO2 removal in acute respiratory failure. In the mid 1980's he worked on the quantitative analysis of thoracic CT imaging, culminating in the "baby lung" (1980's) and lung recruitability (2000's) concepts. In 1990 he was promoted to Full Professor in Anesthesia and Critical Care Medicine at the University of Milan. He has served as Chief of the Department of Anesthesia and Intensive Care since 1986 in Monza and after 1992 in Milan.

He has previously served as President for the Italian National Society of Anesthesia, Analgesia, Resuscitation, and Intensive Care, the European Society of Intensive Care, and the World Federation of Societies of Intensive and Critical Care Medicine. His research is focused on the pathophysiology and treatment of acute respiratory failure, including prone positioning, sepsis and acid base disorders. He has published more than 200 research articles and reviews in peer reviewed journals. Since 1989 he is President of the Smart meeting, which takes place annually in Milan Italy. He is Honorary Member of the German Society of Anesthesiology and Intensive Care, Fellow of the Royal College of Physicians and was awarded with the Life Time Achievement Award by the American Society of Anesthesiology.

Jean-Louis Vincent

Prof Jean-Louis Vincent is Professor of Intensive Care at University of Brussels and an intensivist in the Department of Intensive Care at the Erasme University Hospital, Brussels. He trained as a specialist in internal medicine, including two years at the University of Southern California with Prof Max Harry Weil. Prof Vincent has written more than 800 original articles, 300 book chapters and review articles, and 850 original abstracts, and has edited 86 books.

He is co-editor of the Textbook of Critical Care (Elsevier Saunders, 5th Edition) and the "Encyclopedia of Intensive Care Medicine". He is the editor-in-chief of Critical Care, Current Opinion in Critical Care, and ICU Management. Prof Vincent is member of the Editorial Boards of about 30 journals including Critical Care Medicine, the American Journal of Respiratory and Critical Care Medicine, PLoS Medicine, Lancet Infectious Diseases, Intensive Care Medicine, Shock, and the Journal of Critical Care.

Prof Vincent is presently President of the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM). He is a Past-President of the Belgian Society of Intensive Care Medicine, the European Society of Intensive Care Medicine, the European Shock Society, and the International Sepsis Forum. For 34 years he has organized an International Symposium on Intensive Care and Emergency Medicine which is held every March in Brussels. He has received the Distinguished Investigator Award of the Society of Critical Care Medicine, the College Medalist Award of the American College of Chest Physicians, was the Recipient of the "Society Medal" (lifetime award) of the European Society of Intensive Care Medicine and has received the prestigious Belgian scientific award of the FRS-FNRS (Prix Scientifique Joseph Maisin-Sciences biomédicales cliniques).

John Holcomb

Dr John Holcomb is Professor and Vice Chair of Surgery and Head of the Division of Acute Care Surgery at the University of Texas Health Science Center at Houston. He is also the Director of the Center for Translational Injury Research, a university-wide center focused on translating preclinical research into the clinical arena. Dr. Holcomb is the PI of a T-32 training grant and is involved in education, patient care and research, with interests in trauma, haemostasis, coagulopathy, patient blood management and clinical decision support.

Paul Young

Dr Paul Young is a member of the highly successful Australian and New Zealand Intensive Care Society Clinical Trials Group. He is the director of the Intensive Care Research Programme at the Medical Research Institute of New Zealand and is an Intensive Care Specialist at Wellington Hospital. He established the Intensive Care service at Wakefield Private Hospital in Wellington, where he is the Medical Director. He has extensive experience in investigator-initiated clinical trials in the field of Intensive Care Medicine. He has current research grants totalling more than $15M and has active research collaborations with investigators in Australia, the UK, Italy, Canada, and Scandinavia. He is on the management committee for a number of on-going multinational clinical trials including TARGET (an RCT of 1 kcal/ml vs. 1.5 kcal/ml enteral nutrition); ICU-ROX (liberal vs. conservative oxygen in mechanically ventilated patients); SuDDICU (a cluster trial of selective digestive decontamination); PEPTIC (PPIs vs. HRBs for stress ulcer prophylaxis in ICU); TEAM (an RCT of early activity and mobility); and others. Paul prefers kite surfing to working.

Tim Walsh

Tim Walsh is Professor of Critical Care at Edinburgh University, Scotland and Honorary Consultant in Critical Care at Edinburgh Royal Infirmary, Edinburgh. He is also current head of Department of Anaesthesia, Critical care, and Pain medicine in the Edinburgh University School of Clinical Sciences. He trained in Edinburgh and undertook MD research in the Scottish Liver Transplant Unit, studying oxygen transport during liver transplantation and in acute liver failure. He was appointed consultant in transplantation anaesthesia and intensive care at Edinburgh Royal Infirmary in 1999. Between 1999 and 2011 he was a research active NHS consultant, recognised through an Honorary Chair in Edinburgh University in 2007. In March 2011 he took up the first Chair of Critical Care in Edinburgh University, based in the Centre for Inflammation Research.

He leads a multidisciplinary clinical research group with interests including transfusion medicine, sedation in the critically ill, recovery from critical illness and the epidemiology and prevention of ICU acquired infection. He has authored over 100 original research papers, greater than 25 book chapters, and several evidence based guidelines. He founded the Scottish Critical Care Trials Group and was chair from 2000-2013. He is Chair of the National Institute of Healthcare Research Comprehensive Clinical Research Network Specialty Group for Critical Care, which oversees the UK portfolio of Critical Care Research. Other roles include membership of the UK Intensive Care Leadership Forum, and a range of advisory roles relevant to intensive care research.

Anthony Gordon

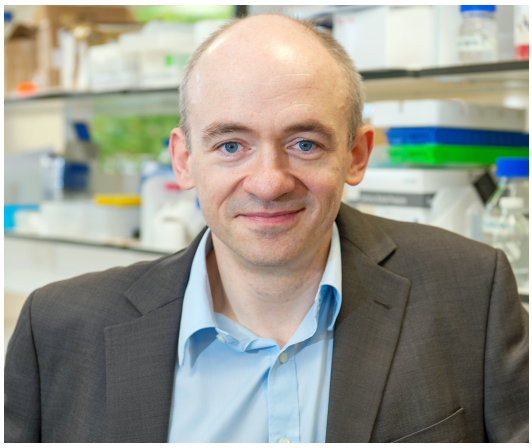
Dr Gordon is a Reader and Consultant in Critical Care Medicine at Imperial College / Charing Cross Hospital. He trained in anaesthesia and intensive care medicine in the North West Thames region and obtained his MD at St Bartholomew's. He has also worked at the Royal North Shore Hospital in Sydney, Australia and St Paul's Hospital, Vancouver, Canada.

Dr Gordon was an NIHR Clinician Scientist and is a Director of Research for the Intensive Care Foundation. He is the Chief Investigator for two UK multi-centre septic shock trials (VANISH and LeoPARDS) and is part of the UK Critical Care Genomics group.

Brian Burns

Dr Brian Burns is an Emergency Physician and Prehospital & Retrieval Specialist in Sydney, Australia. In the addition to his clinical duties, Brian is the Research Director for Sydney HEMS, Director of Trauma, Orange Health Service, New South Wales and Assistant Professor of Emergency Medicine at the University of Sydney. Brian's clinical interests include prehospital trauma, resuscitation and ECMO.

Danny McAuley



Danny McAuley is Professor and Consultant in Intensive Care Medicine at the Royal Victoria Hospital and Queen's University Belfast. He graduated from Queen's University Belfast in 1992, after which he trained in Belfast, Birmingham, London and San Francisco. Danny is currently Director of the Northern Ireland Clinical Research Facility and the Northern Ireland Clinical Trials Unit, Co-Director of Research for the UK Intensive Care Society and Chair of the Irish Critical Care Trials group. He has two main research interests; acute lung injury and clinical trials. Danny is involved in multiple studies, with his next large project being the Rest Study (pRotective vEntilation with veno-venous lung assisT in respiratory failure). He has also supervised many wonderful PhD students.

Rob Mac Sweeney

Rob Mac Sweeney is an intensivist in the the Royal Victoria Hospital in Belfast, and runs Critical Care Reviews in his spare time. This began as a free online critical care literature website in 2009, but has gradually developed into a multi-faceted project spanning website, weekly newsletter, annual meeting, plus a planned annual book and a imminent podcast.

With Andrew Ferguson, Rob co-founded, and is the current Editor-in-Chief of, *Critical Care Horizons*, a genuine open access critical care journal which is free to publish with and free to read. The first issue was published last Summer.

Chairs

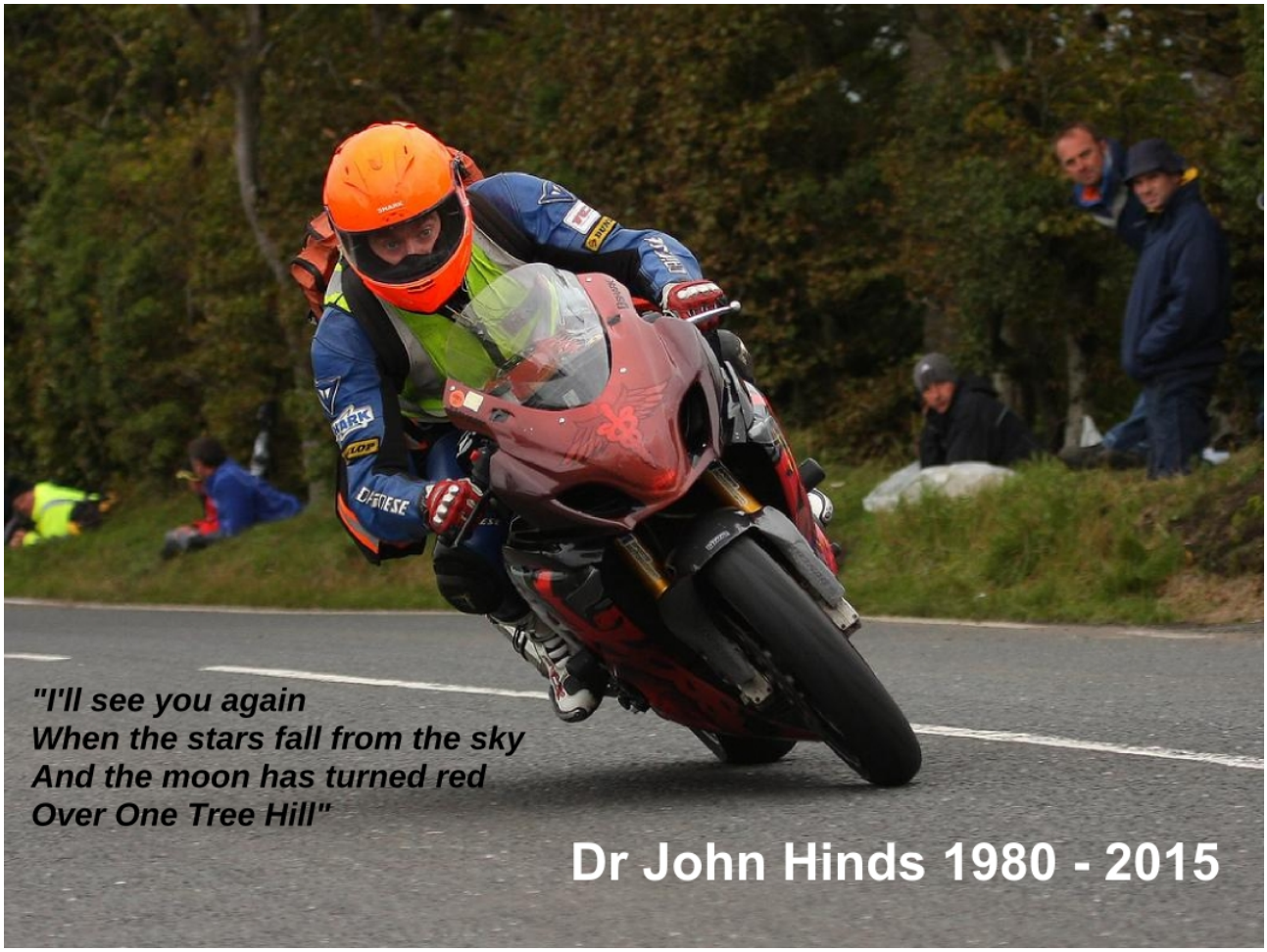
Dr Anna Batchelor	- Consultant in Intensive Care Medicine and Anaesthesia, Royal Victoria Infirmary, Newcastle - Dean of the Faculty of Intensive Care Medicines
Dr Rosalind O'Reilly	- Specialist Registrar in Intensive Care Medicine and Anaesthesa, Northern Ireland School of Anaesthesia
Dr John McCaffrey	- Consultant in Intensive Care Medicine and Anaesthesia, Belfast City Hospital - President, Northern Ireland Intensive Care Society
Dr Michelle Fallon	- Specialist Registrar in Anaesthesia, Northern Ireland School of Anaesthesia
Dr Ganesh Suntharalingam	- Consultant in Intensive Care Medicine and Anaesthesia, Northwick Park Hospital, London - Lead Organiser, Intensive Care Society State-of-the Art Meeting
Dr Marianne Fitzgerald	- Doctoral Fellow, Centre for Infection and Immunity, Queen's University Belfast - Specialist Registrar in Anaesthesia

Dr John Hinds

Last July, Northern Ireland lost one of its leading intensivists, anaesthetists and pre-hospital clinicians. John Hinds was just 35 years old when he died at the Skerries 100 Road Race, providing medical cover for the sport he loved. His life, like his career, was tragically cut short in his prime.

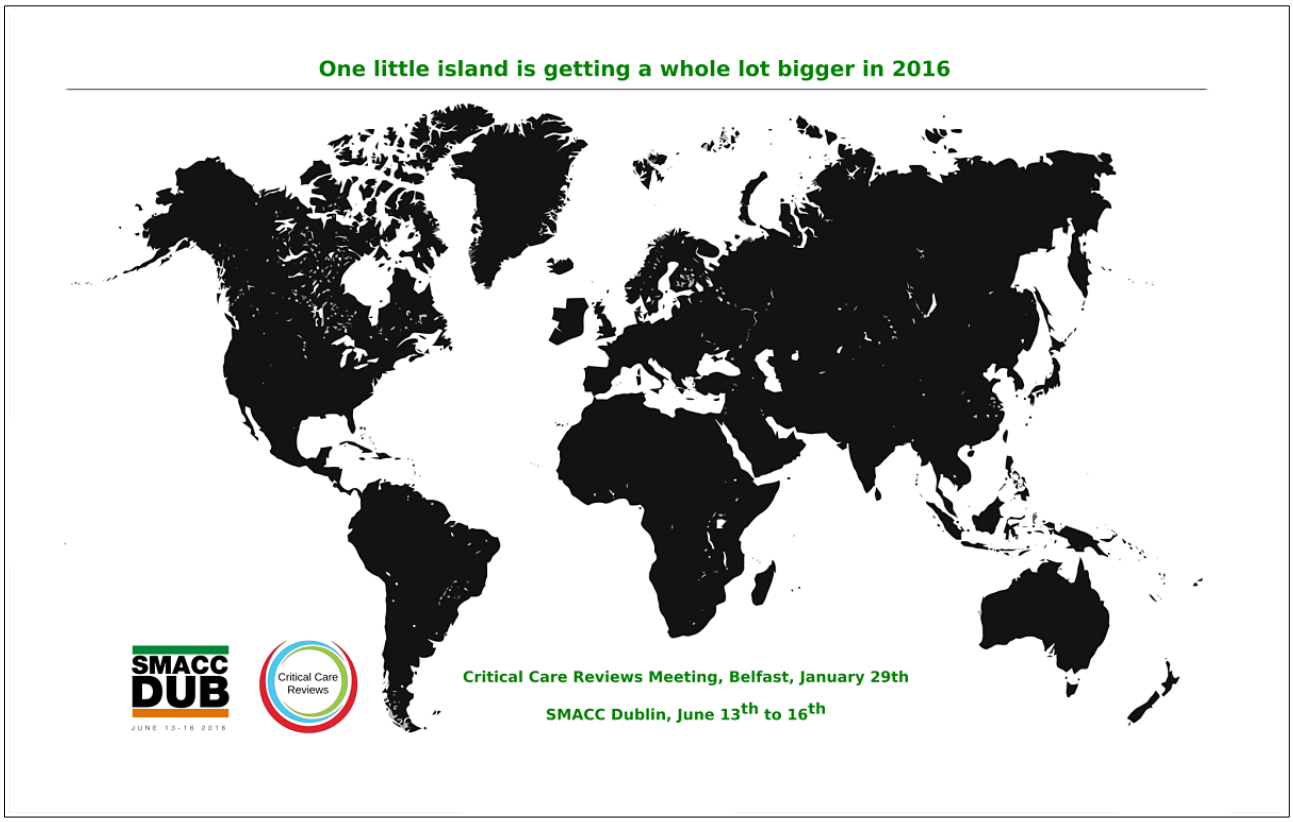
Through his entertaining and thought-provoking talks at successive SMACC conferences in Australia and the USA, John had become a global figure in the world of critical care. At home, he was already renowned for his pre-hospital work on the motor-biking circuit, where he had many friends and was highly respected. It was his public profile which helped drive the call for a Helicopter Emergency Medicine Service for Northern Ireland, a project to which he was deeply committed, and which is on the cusp of being delivered. As an anaesthetist and intensivist in Craigavon Area Hospital, John provided first class care to all whom he cared for.

It is with great sadness and pride that today we begin the inaugural John Hinds Trauma Lecture, contributing to his legacy of improving trauma care for everyone, everywhere. It is fitting his great friend Dr Brian Burns has travelled from Sydney, Australia to deliver the first oration.



SMACC Dub

The global critical care festival that is the SMACC (Social Media and Critical Care) Conference comes to Dublin in just five months time. With the first two batches of registrations selling in just a few hours and minutes, respectively, this conference is the hottest ticket in town especially considering it may not return to Europe for several years. If you haven't yet registered, the final tickets go on sale on Tuesday February 2nd and will be available at www.smacc.au.net.



With an emphasis on entertaining, data light, concept heavy presentation styles, and an international multi-disciplinary faculty from the worlds of academia and social media, this is a conference with a difference. If you are unlucky enough to miss out, all talks are recorded and made freely available on the Intensive Care Network website (www.intensivecarenetwork.com).

Consistent with its origins in the altruistic world of the free open access medical education (FOAMed) movement, the SMACC organisers have channelled the profits from previous meetings into their C4 Charity (Centre for Critical Care Collaboration), supporting the work of other not-for-profit critical care educational organisations. The Critical Care Reviews Meeting 2016 has been the recipient of an unrestricted grant from C4, as well as other financial support and ongoing expertise.

See you in Dublin in June.

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SISK healthcare

Studies of Note

As a meeting aiming to review the biggest studies of the previous year, we are limited in the number of investigations we can discuss in detail on the day. Although we will briefly mention many other studies of note during the meeting, over the next 180 pages of this meeting booklet we have provided a more in-depth critique of some of these trials.

These reviews follow a three part model – a study synopsis, a critique and a consideration of how the trial sits with the remaining body of evidence in that particular field. Each review is intended to "stand alone", and can be read in isolation from the remaining reviews. As such, there is a degree of repetition in reviews of studies examining similar topics.

These reviews are a trial run for what we hope will be a much more complete separate book next year. As a trial version, this is not inclusive of all the major studies of 2015. There are many large studies we would like to have included, but weren't able to do so.

Comments and criticisms will be gratefully received to help us make next year's book something you would like to have. Ideally, we'll aim to make the 2017 edition freely available if possible. We hope you find this year's trial useful.

These studies are listed on the meeting webpage (www.bit.do/CCR16) and include links to the original publication.

Contributors

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Abbreviations used:

95% confidence interval	95% CI
Relative risk	RR
Odds ratio	OR
Hazard ratio	HR
Intensive care unit	ICU

The HEAT Trial

Young P, Saxena M, Bellomo R, Freebairn R, Hammond N, van Haren F, et al. Acetaminophen for Fever in Critically Ill Patients with Suspected Infection. New England Journal of Medicine. 2015 Dec 3;373(23):2215–24.

Study synopsis

This multi-centre, blinded, randomised, controlled trial compared the effect of paracetamol (acetaminophen) with placebo in ICU patients with fever and probable infection. The investigators hypothesised paracetamol was harmful and would result in fewer ICU-free days. ICU patients were eligible if they were aged ≥ 16 years, had a temperature of ≥ 38°C within 12 hours prior to enrolment and had known or suspected infection treated with antimicrobials.

The intervention consisted of 1 g of intravenous paracetamol (Perfalgan®, Bristol-Myers Squibb) or a placebo of 5% dextrose in water in identical glass bottles, every 6 hours. The intervention was continued until day 28, discharge from ICU, resolution of fever (temperature < 37.5°C for 24 hours), cessation of antimicrobials or death. Physical cooling was permitted as a rescue therapy in cases of temperature ≥ 39.5°C. NSAID use (other than aspirin) was contraindicated. Open label paracetamol use was permitted after the course of study medication was completed.

The primary outcome measure was the number of ICU-free days (alive and discharged from ICU) in the first 28 days. Patients who died were assumed to have zero ICU-free days. Based on previous data, a mean value of 16.0 ± 9.2 ICU-free days was assumed. A sample size of 700 patients was required to give an 80% power to detect a difference of 2.2 ICU-free days in the 28 days after randomisation, at an alpha level of 0.05.

700 patients were enrolled from 23 adult ICUs in Australia and New Zealand. Ten patients withdrew consent, leaving 690 patients in the final intention-to-treat analysis; 346 randomised to paracetamol and 344 to placebo. The groups were well balanced, and the commonest site of infection was the lungs. The mean time from ICU admission to randomisation was 1.3 ± 1.8 days in the paracetamol group and 1.4 ± 2.3 in the placebo group. The peak temperature in the 12 hours before randomisation was similar; 38.8 ± 0.6°C and 38.7 ± 0.6°C in the paracetamol and placebo groups, respectively.

The median number of doses of study drug administered in the paracetamol group was 8 (IQR 5 - 14) compared to 9 (IQR 6 - 15) in the placebo group (absolute difference, −1 dose; 95% CI, −2 to 0; P = 0.15). The study drug was discontinued due to resolution of temperature in 22.8% of the paracetamol group and 16.9% of the placebo group (odds ratio, 1.45; 95% CI, 0.99 to 2.12; P = 0.05). The study drug was discontinued due to ICU discharge in 45.5% of the paracetamol group and 47.4% of the placebo group.

Patients in the paracetamol group had a lower mean daily peak body temperature compared to those treated with placebo (38.4 ± 1.0°C vs. 38.6 ± 0.8°C; absolute difference, −0.25°C; 95% CI, −0.38 to −0.11; P < 0.001) and also a lower mean daily average body temperature (37.0 ± 0.6°C vs. 37.3 ± 0.6°C; absolute difference, −0.28°C; 95% CI, −0.37 to −0.19; P < 0.001).

There was no difference in the primary outcome measure of ICU-free days; 23 and 22 days in the paracetamol and placebo groups respectively (absolute difference, 0 days; 96.2% CI, 0 to 1; P = 0.07). There was no difference in ICU-free days in any of the pre-specified subgroup analysis. There was no difference in a number of secondary outcomes, including 28- or 90- day mortality, or survival time to day 90. There was no difference in ICU or hospital length of stay. However, there was heterogeneity of response, with paracetamol associated with a shorter length of stay in survivors (3.5 days [IQR, 1.9 to 6.9] vs. 4.3 days [IQR, 2.1 to 8.9], P = 0.01), and a longer ICU length of stay in non-survivors (10.4 days [IQR, 4.1 to 16.9] vs. 4.0 days [IQR, 1.7 to 9.4], P < 0.001).

Critique

This is an excellent paper and surely one of the most thought provoking of the year. It is unknown whether fever induces further physiological stress in an already critically ill patient or whether it represents a protective mechanism that should be left untreated. While many interesting discussion points on the use of paracetamol and the management of fever arise from this paper, it also adds to the wider discussion of whether “euboxia” (aiming for normality in ICU) is beneficial.

In sepsis, immune system activation via Toll-like receptor 4 (TLR-4) results in the production of the interleukins IL-1β and IL-6, and tumour necrosis factor (TNF)-α. These pyrogenic cytokines activate the cyclo-oxygenase-2 (COX-2) system with subsequent release of prostaglandin E_2 (PGE_2). PGE_2 results in increased heat production via alteration of the hypothalamic temperature set point. Heat shock proteins protect human cells from degradation at times of pyrexia. In the temperature range 38 °C – 40 °C, neutrophil, lymphocyte and macrophage function is enhanced. At ≥ 41°C, neutrophils and macrophages show reduced function. Pyrexia inhibits the function of organisms such as influenza virus, Streptococcus pneumonia and Neisseria meningitidis.[1]

In 1917 the Austrian psychiatrist Julius Wagner Jauregg recognised that patients with neurosyphilis often became sane after a bout of fever. This led him to inoculate patients with malaria to induce fever. Once cured of their neurosyphilis, patients had their malaria treated with quinine sulphate.[2] In an observational study by Young and colleagues of 600,000 intensive care patients, pyrexia was found to be associated with a decrease in mortality.[3]

The HEAT trial was a well conducted, multi-centre, randomised, placebo controlled trial

with excellent follow up rates. The discussion points relate to the low doses of paracetamol given, the contamination between groups and the potential immunomodulatory effect of paracetamol.

The total paracetamol dose that patients received was low at 8 grams. Additionally, the treatment duration was short. In the paracetamol group, 81% of patients received the drug in accordance with the protocol and 11.5% of doses were missed. The number of patients in both groups that had open label paracetamol was high at approximately 30%. This may have diluted the treatment effect. Also, it was not known how many patients had paracetamol prior to randomisation.

There was no difference in overall length of stay, but for those in the paracetamol group this was due to a combination of shorter length of stay in survivors and a longer length of stay in non-survivors. This overall lack of difference should not detract from the finding that ICU length of stay was shorter for survivors treated with paracetamol. Indeed, the finding of reduced length of stay for survivors and increased length of time for the non-survivors in the paracetamol group is one of the most thought provoking aspects of this paper. There was a only small difference in mean temperature (0.3 °C) and peak temperature (0.4 °C) between the two groups. Although these were statistically significant, it may not have been enough to account for the changes in length of stay and a delay in death. This delay in death is consistent with a large retrospective review looking at the use of paracetamol in ICU and also a paper looking at physical cooling in septic shock.[4,5]

This paper adds to the hypothesis that paracetamol has an immunomodulatory effect. The low number of doses and short duration of treatment with paracetamol may have contributed to the lack of a positive result in this study. Further work may require the use of regular paracetamol for a prolonged duration to improve the chances of identifying a treatment effect.

Where it sits in the body of evidence

- A retrospective observational study reviewed 15,818 patients over a 12 year period in four Australian ICUs.[4] 64% of patients received at least one gram of paracetamol. Patients who received paracetamol had a higher mean temperature and were more likely to have a pyrexia than those who did not receive paracetamol. Patients who received any paracetamol had a lower in-hospital mortality (10% vs. 20%, P <0.001). Using a multivariate logistic regression analysis, an independent association was identified between the use of paracetamol and a reduced in-hospital mortality (adjusted OR, 0.60; 95% CI, 0.53 to 0.68, P < 0.001). This association was lost after adjustment for pyrexia. In a finding similar to the HEAT trial, there was an association between paracetamol and increased time to death.

- In a multi-centre, randomised controlled trial, external cooling was compared with standard therapy in 200 patients with septic shock requiring vasopressor support and mechanical ventilation.[5] There was good separation of temperatures between the two groups at two hours (36.8 ± 0.7°C vs. 38.4 ± 1.1°C; P = 0.01). A 50% reduction in vasopressor dose at twelve hours was more common with external cooling (54% vs. 20%; absolute difference, 34%; 95% CI, -46% to -22%; P = 0.001). However, there was no difference in the primary endpoint of number of patients achieving a 50% vasopressor dose reduction at 48 hours. Mortality at day 14 was a secondary endpoint and was significantly lower in the cooling group (19% vs. 34%; absolute difference, –16%; 95% CI, -28% to -24%; P = 0.013).

- The effect of a variety of antipyretic treatments was studied in a prospective observational study of 1,425 ICU patients with fever due to any cause.[6] In patients with sepsis, the use of NSAIDs was associated with an increase in 28-day mortality (adjusted OR, 2.61; P = 0.028), as was the use of paracetamol (adjusted OR, 2.05, P = 0.01). There was no difference in patients without sepsis. Physical cooling was not associated with a change in mortality, in either septic or non-septic patients.

- A study of over 600,000 critically ill patients (including a derivation cohort from Australia and New Zealand and a validation cohort from the UK) looked at the effect of temperature on mortality.[3] Baseline mortality was derived from those with a peak temperature of 36.5 °C – 36.9 °C. Those with a peak temperature of 39 °C – 39.4 °C were at the lowest risk of death (adjusted OR, 0.56; 95% CI, 0.48 to 0.66). In non-septic patients, the mortality risk increased with increasing temperature (adjusted OR, 2.07 at 40.0°C or above; 95% CI, 1.68 to 2.55).

- A further study looked at the effect of temperature in critically ill patients.[6] For non-septic patients with a maximum temperature of 38.5 °C – 39.4 °C the odds ratio for 28-day mortality was 5.13 (P < 0.007). For a maximum temperature ≥ 39.5 °C the odds ratio was 13.4 (P < 0.001).
- In critically ill patients, an observational study showed paracetamol (predominantly via the oral route) had only a modest effect on the rate of cooling (mean 0.20 °C per hour compared to 0.13 °C per hour for untreated fevers (95% CI of the difference, -0.1107 to -0.01204; P = 0.0152).[7]

- One hundred and two patients with acute ischaemic stroke were randomised to either one gram of paracetamol or placebo every 6 hours.[8] Patients treated with paracetamol had a mean body temperature within 4 hours of treatment 0.26 °C lower than those treated with placebo (95% CI, 0.07 °C – 0.46 °C).

- In a small study of 79 pyrexial neurocritical care patients, a combination of paracetamol and ibuprofen was found to be more effective in temperature reduction

that paracetamol alone.[9] The difference in temperature reduction for ibuprofen plus paracetamol, compared to paracetamol alone, was 1.56 °C per hour (P = 0.03).

- In a small trial, patients with acute traumatic brain injury were randomised to receive 6g of IV paracetamol per day (n = 21) or placebo (n = 20) for 72 hours.[10] There was no difference in the mean temperature between the two groups (37.4 ± 0.5 °C in the paracetamol group vs. 37.7 ± 0.4°C in the placebo group (absolute difference -0.3°C; 95% CI, -0.6 to 0.0, P = 0.09).

Should we implement this into our practice?
This is unclear. It would seem pyrexia is protective in sepsis. Whether paracetamol improves outcomes via a mechanism other than temperature modulation requires more work. Paracetamol appears to have only a modest anti-pyretic effect.

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The PROPPR Trial

Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015 Feb;313(5):471–82.

Study synopsis

This trial evaluated the safety and effectiveness of transfusing plasma, platelets and red blood cells (RBCs) in a 1:1:1 ratio, compared to a 1:1:2 ratio, in severely injured patients. This was a pragmatic, randomised controlled trial carried out in 12 level 1 trauma centres in North America.

Severely injured patients were identified at each centre using site-specific criteria based on heart rate, blood pressure, respiratory rate, and mechanism of injury. Patients were recruited if they met any one of the following criteria: need for any blood products pre-hospital or within the first hour of hospital admission, an Assessment of Blood Consumption score ≥ 2, or predicted to need massive transfusion by the treating physician.[1]

Containers of blood products were prepared by blood bank and transfused in a prescribed order. The 1:1:1 group were provided with a container which included 1 dose of platelets (which was approximately a pool of 6 units), 6 units of RBCs and 6 units of plasma. Patients randomised to this group received 1 unit of platelets first, followed by alternating units of RBCs and plasma.

The 1:1:2 group were provided initially with a container of 6 units of RBCs and 3 units of plasma, but no platelets. Patients received two units of RBCs followed by 1 unit of plasma until a total of 6 units of RBCs and 3 units of plasma had been transfused. If further blood products were needed a second container was provided with 1 unit of platelets, 6 units of RBCs and 3 units of platelets. Platelets were transfused first, followed by 2 units of RBCs and 1 unit of plasma as before. All even numbered containers contained platelets.

The transfusion protocol was ceased if no further blood products were needed, haemostasis was achieved, treatment was deemed futile, the patient died or there was a protocol violation. Treating clinicians could not be blinded but assessors were. The primary outcome measures were differences in mortality at 24 hours and 30 days. Secondary outcomes included time to haemostasis and blood product utilisation. Haemostasis was defined as bleeding judged to be controlled by the operating surgeon or no contrast blush after radiological embolisation.

The 680 patients in this trial had a median Injury Severity Score of 26, with 75% of patients requiring surgery or an interventional radiology procedure within two hours of admission. During the intervention period, there was good separation in use of blood products between the two groups. For the use of *plasma,* patients in the 1:1:1 group achieved a plasma:RBC ratio of 1:1, whereas those in the 1:1:2 group achieved a ratio of 1:2. For the use of *platelets,* patients in the 1:1:1 group achieved a platelet:RBC ratio of 1.5:1, whereas those in the 1:1:2 group achieved a ratio of 1:2.5.

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.

Critique

This is one of the landmark studies of the year. The scale of this undertaking can be understood when one realises that 78% of all trauma cases, totalling 14,313 patients, were screened at the 12 study sites. An Injury Severity Score of 26 plus a requirement for an operative intervention within 2 hours in 75% of patients demonstrates the level of critical illness in this study.

Retrospective observational studies have shown that trauma patients requiring massive transfusion had increased 30-day survival if they received a high plasma:RBC ratio (> 1:2) or a high platelet:RBC ratio (> 1:2), in comparison to those who received low ratios (< 1:2).[2] However, it is unclear whether this represents a treatment effect or a survival bias. 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.[3]

In recruiting 680 patients, the study was powered to detect a > 10% difference in 30-day mortality. The power calculations were based on observational work by Holcomb and colleagues which had shown patients with higher ratios of plasma and platelets had a 20% reduction in 30-day mortality.[2] The observed mortality of 22.4% in the 1:1:1 was almost identical to predicted mortality of 23% upon which the power calculations were based. However, the observed mortality of the 1:1:2 group was much lower than expected (26.1% instead of 35%). The investigators comment that 2,968 patients would be needed to detect the 4.2% 24 hour mortality difference seen between these groups.

The shorter time to haemostasis and reduced death from exsanguination suggest there may be benefit in the 1:1:1 strategy. However, a larger study would be needed to confirm this.

Better than expected outcomes in the 1:1:2 group were responsible for this study being "underpowered". Patients in the 1:1:2 group were randomised by a median time of 25.5 minutes, with containers of blood products (including plasma) being delivered to the bedside within 10 minutes. This efficient service may not be representative of usual care in many hospitals. It may be that patients in the 1:1:2 group received plasma much earlier than previously observational studies, hence improving the outcomes (in the PROMMTT trial approximately 1 in 5 had not received plasma at 2 hours).[3] This leads to the question, if the "control" group received usual care (e.g. transfusions based on laboratory findings) would a treatment effect have been seen?

It is notable the overall use of tranexamic acid was low (approximately 19%), although this was similar in both groups. The 1:1:2 group received more blood products in the post intervention period, with a number of outliers requiring large volumes of platelets. Treating clinicians were unblinded, so this may represent a source of bias or simply a response to clinical need. This phenomenon of "catch up" may have diluted the treatment benefit of the 1:1:1 strategy.

Platelets were given first in the 1:1:1 group and the platelet ratios were very different between the groups (1.5:1 in the 1:1:1 group versus 1:2.5 in the 1:1:2 group). The difference in plasma use was less striking (see table). It could be argued this was as much a trial about early platelet use as a trial about transfusion ratios. This raises the question; is the overall transfusion ratio the most important aspect of care or is simply giving plasma and platelets enough? More work needs to be done.

Resuscitation up to 24 hours	1:1:1 group (N = 338)	1:1:2 group (N = 342)	p-value
Plasma (median no. units)	7	5	< 0.001
Platelets (median no. units)	12	6	< 0.001
RBC (median no. units)	9	9	0.30

Where it sits in the body of evidence

- The PROMMTT study was a prospective, observational study examining the effects of transfusion ratios in trauma.[3] In a study of 1,245 patients closely mirroring the demographics of the PROPPR study population, 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.[3] By eight hours 84% of patients had a plasma:RBC ratio of greater then 1:2, and 80% had a platelet:RBC ratio of greater than 1:2.

- The CRASH-2 trial involved 20,211 trauma patients who were deemed at risk of significant bleeding. Patients were randomised to receive either tranexamic acid or placebo.[4] Patients who received tranexamic acid had a reduced 28 day all cause mortality (relative risk, 0·91; 95% CI, 0·85 to 0·97, P = 0·0035). Death due to haemorrhage was also reduced (relative risk, 0·85; 95% CI, 0·76 to 0·96, P = 0·0077). There was no treatment benefit if tranexamic acid was administered after 3 hours. Interestingly, there was no difference in transfusion requirements between the two groups, forcing the question as to the mechanism of action of tranexamic acid. The study was also largely conducted in health care systems without the capabilities of most modern Western trauma services.

- In a retrospective study of 896 patients who had sustained combat injuries, the MATTERs study reported reduced mortality in those who had received tranexamic acid compared those who had not (17.4% vs 23.9%, respectively; P = 0.03).[5] This was despite patients in the tranexamic acid group being more severely injured (Injury severity score 25.2 vs 22.5).

- The MATTERs II trail was an observational analysis of 1,332 trauma patients from Afghanistan and examined the role of tranexamic acid and cryoprecipitate, either in isolation or in combination.[6] Patients who received tranexamic acid *and* cryoprecipitate had the lowest associated mortality (11.6%), followed by those who received tranexamic acid alone (18.2%), then cryoprecipitate alone (21.4%) and then neither tranexamic acid or cryoprecipitate (23.6%).

- In the *New England Journal of Medicine* in 1994, Bickell and colleagues published a seminal single centre study looking at delayed fluid resuscitation for penetrating torso injuries.[7] Patients with a penetrating torso injury were randomised to either immediate resuscitation (IV fluid resuscitation with a target systolic BP of 100mmHg) or delayed resuscitation (no fluids until operative intervention). Survival to hospital discharge was higher in the delayed resuscitation group (70% vs 62%, P = 0.04). In this study 1,069 patients were recruited but only 598 were analysed, the remainder were excluded as they had either minor injuries or a revised trauma score of zero.

- Dutton and colleagues randomised 110 patients with either blunt or penetrating trauma to a target systolic BP of 70mmHg or 100mmHg.[8] Although there was no

difference in survival, any treatment effect would have been limited by poor blood pressure separation between the two groups.

- The Assessment of Blood Consumption (ABC) score was devised to predict the need for massive transfusion based on four equally weighted parameters; systolic BP < 90 mmHg, heart rate > 120 BPM, penetrating injury and positive Focused Assessment Sonography for Trauma.[9] The predictive value was good, with an AUROC of 0.842. An ABC score of 2 or greater had a 75% sensitivity and 86% specificity for predicting the need for massive transfusion.

- The CONTROL trial attempted to evaluate the effects of recombinant activated factor VII.[10] It was terminated early, after 573 of a planned 1,502 had been enrolled, due to lower than expected mortality and perceived futility.

Should we implement this into our practice?
Maybe. Although the primary outcome was similar between groups, important secondary outcomes were in favour of the 1:1:1 ratio group. Also, the 1:1:2 group effectively "caught up" with blood product administration, further reducing the difference in therapeutic strategies under investigation. This study supports a low ratio transfusion strategy for traumatic haemorrhage.

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The SPLIT Trial

Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, et al. Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. JAMA 2015;314(16):1701-10

Study synopsis

SPLIT was a double-blind, cluster randomized, double-crossover trial conducted in 4 ICUs in New Zealand in 2014, and compared the effect of a buffered crystalloid (Plasma-lyte 148) with 0.9% saline on renal complications in ICU patients. Pre-clinical and observational studies suggest unbalanced solutions, such as 0.9% saline, which has a high chloride content, are associated with the development of hyperchloraemia, renal hypoperfusion and acute kidney injury (AKI). All patients admitted to ICU and requiring crystalloid fluids were eligible for inclusion in this study, with end-stage renal failure and a need, or likely need, for renal replacement therapy being exclusion criteria. Patients admitted to ICU for consideration of organ donation or palliation were similarly excluded.

Blinded study fluids were used in each ICU for alternating 7 week blocks, with two ICUs using Plasma-lyte and two using saline at any time. The initial choice of fluid was determined by computer-generated randomization. Fluids were provided in identical 1,000 ml bags labelled as “fluid A” or “fluid B”, with patients continuing on their original fluid if their ICU stay traversed a 7 week study block. Study fluid was used for all fluid administration purposes, unless a specific requirement for saline or Plasma-lyte arose. The primary outcome measure was the proportion of patients with AKI, defined as “injury or greater” on the RIFLE score, based solely on creatinine value. There were numerous secondary outcomes, as well as five pre-defined subgroups. There was no pre-determined sample size, due to the temporal design of the study. Analysis was performed on an intention-to-treat basis.

All 2,278 eligible patients were enrolled, with 1,162 patients randomized to Plasma-lyte and 1,116 patients randomized to saline. Over 99% of both groups were analysed. The mean patient age was 60 years and two thirds were men. Most patients were post elective surgery, mostly cardiovascular surgery, with few with co-morbidities. Both groups were well balanced, and had identical mean APACHE II scores of 14.1. Both groups received similar median volumes of study fluid; Plasma-lyte 2,000 mL versus saline 2,000 mL (P = 0.63). The majority of fluid was administered in the first day.

There was no difference in the primary outcome of the development of AKI within 90 days; Plasma-lyte 9.6% vs saline 9.2% (absolute difference, 0.4%; 95% CI, −2.1% to 2.9%; RR, 1.04; 95% CI, 0.80 to 1.36; P = 0.77). Similarly, there were no differences in the

probability of requiring renal replacement therapy (RRT) within 90 days (Plasma-lyte 3.3% versus saline 3.4%; P=0.085), or development of AKI in the predefined subgroups. The indications for RRT were similar between groups also, with no patients requiring prolonged RRT. There were no differences in resource utilisation (days in ICU, days in hospital, mechanical ventilation requirement, ICU readmission) or mortality, including death in ICU (6.6% vs 7.2%; P=0.62) or death in hospital (7.6% vs 8.6%; P=0.40).

Critique

SPLIT is a landmark ICU trial for many reasons. Firstly, it is a remarkable achievement to complete a 2,278 patient study in just 28 weeks for a fraction of the cost of a similar sized individual patient RCT. Secondly, even allowing for an opt-out, rather than opt-in, recruitment policy, it is impressive to have all eligible patients recruited and over 99% of patients analysed. Thirdly, SPLIT demonstrates trials of this nature are achievable, delivering important answers on important questions. Fourthly, it is important to remember the SPLIT study is a pilot study, and as such, quickly provides necessary preliminary data without the robustness of a formal individual patient randomised controlled trial. A cluster randomised, double-crossover trial design is also more difficult to statistically analyse.

As with any study, this investigation has its limitations, although remarkably few. Firstly, the delivered dose of fluids is low, reducing the opportunity to truly affect the underlying physiology and induce significant electrolyte or acid-base disorders. To run a study of this size, for this cost, minimises the ability to measure as many variables as ideally would be done. Plasma electrolytes values were casualties of this approach, impeding an inquisition into possible mechanisms of chloride toxicity. Similarly, while the low fluid dose may have minimised the development of a difference in patient physiology, a relatively well elective surgical population further reduced the impact of any modest physiological perturbations which may have occurred.

The choice of Plasma-lyte, which is commonly used in New Zealand, raises the question of the generalisability of the results of this study to regions which use alternative balanced crystalloids, such as Hartmann's solution.

Many of these criticisms have informed the design of the follow-on PLUS study (Plasma-lyte versUs Saline), an 8,800 randomised controlled trial in a sicker population of ICU patients. These adult patients will require fluid resuscitation, be expected to be in ICU for at least three days and unable to take oral fluids. Such a cohort has an expected baseline mortality of 23%. The primary endpoint is mortality at 90 days. We look forward to watching this study closely.

Where it sits in the body of evidence

- There have been several randomised controlled fluid trials in critically ill patients over

the past 15 years, largely comparing various crystalloid solutions with colloid solutions, such as the SAFE, CHEST and 6S trials.[1–3] While these help inform decision regarding the appropriateness of colloid administration in the critically ill, they are of little help in answering the question as to whether to use a balanced or unbalanced crystalloid, as both fluids being compared usually contain unbalanced solutions. Other than SPLIT, there is little quality evidence available on this topic.

- Raghunathan and colleagues completed a retrospective cohort study, examining 3,396 patients with septic shock treated with vasopressors and crystalloids, including a propensity-matched cohort of 6,730 patients, and found receipt of balanced crystalloids was associated with lower in-hospital mortality (19.6% vs 22.8%; RR, 0.86; 95% CI, 0.78 to 0.94).[4] There were no significant differences in the prevalence of acute renal failure (with and without renal replacement therapy) or in-hospital and ICU lengths of stay. Mortality was progressively lower among patients receiving larger proportions of balanced fluids.

- Yunos and colleagues performed an open-label, before-and-after pilot study in 760 consecutive ICU patients, comparing a six month period of standard intravenous fluid administration with a six month period limited to chloride poor intravenous fluid administration only.[5] There was a significant decrease in chloride administration from the first to second periods, from 694 to 496 mmol / patient, which was associated with a concomitant lesser level of creatinine rise from period one to two; 22.6 μmol/L (95% CI, 17.5 to 27.7 μmol/L) vs 14.8 μmol/L (95% CI, 9.8 to 19.9 μmol/L) (P = 0.03). Similarly, there was a reduced incidence of both RIFLE-defined AKI; 14% (95% CI, 11% to 16%; n = 105) vs 8.4% (95% CI, 6.4% to 10%; n = 65) (P < 0.001), and use of RRT 10% vs 6.3% (P = 0.005). Interestingly, these findings failed to translate into summary patient-centred outcomes, such as hospital mortality, hospital or ICU length of stay, or need for RRT after hospital discharge. Before-and-after studies are prone to residual confounding and it has been suggested the difference seen may have been due to the standard intravenous fluid group being exposed to a significant volume of gelatin solution, a fluid with an unknown safety profile and which has never been licensed in the USA.

- Potura and colleagues randomised 150 recipients of a cadaveric renal transplant to perioperative management with either unbalanced 0.9% saline, with a potential base excess of -24 mmol/L, or a chloride-reduced, acetate-buffered balanced crystalloid (Elomel Isoton , Fresenius Kabi, Austria, GmbH), with a potential base excess of 0 mmol/L).[6] Despite receiving similar median amounts of fluid; saline 2,625 mL vs buffered crystalloid 2,500 mL (P = 0.83), saline administration resulted in higher chloride levels; 109 mmol/L (IQR, 107 to 111) vs 107 mmol/L (105 to 109); P < 0.001 and more acid-base disturbance; base excess −4.5 mmol/L (−6 to −2.4) vs −2.6 mmol/L (−4 to −1), respectively; P < 0.001. Saline administration also resulted in double the

requirement for catecholamine support (30% vs 15%, P = 0.03). There was no difference in the primary outcome of incidence of hyperkalaemia, 17% vs 21%; P = 0.56.

- O'Malley and colleagues also undertook a randomised controlled in the renal transplant setting, comparing lactated Ringers with 0.9% saline in 54 patients.[7] Both groups received similar volumes of fluid: lactated Ringers 5.6 ± 1.4 L and saline 6.1 ± 1.2 L. Colloid was not used in the study. The study was terminated early for safety reasons, after analysis of 51 patients (3 were excluded for hyperkalaemia). There was no difference in the primary outcome of serum creatinine on the third post operative day. Five patients (19%) in the saline group versus no patients in the lactated Ringers group had potassium concentrations > 6 mmol/L and were treated for hyperkalaemia (P = 0.05). Eight patients (31%) in the saline group versus no patients in the lactated Ringers group were treated for metabolic acidosis (P = 0.004).

Should we implement this into our practice?
Yes. Saline appears reasonably safe at a low dose in a relatively well population. Whether it is safe at a larger dose in a sicker population is unanswered. With signals of harm from other studies, it requires a strong rationale for its use in such patients.

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The Eurotherm 3235 Trial

Andrews PJD, Sinclair L, Rodriguez A, Harris BA, Battison CG, Rhodes JKJ, et al. for the Eurotherm3235 Trial Collaborators. Hypothermia for Intracranial Hypertension after Traumatic Brain Injury. New England Journal of Medicine. 2015 Dec 17; 373; 25:2403-12.

Study Synopsis

This was a multi-centre, randomised trial at forty seven sites in eighteen countries. The aim was to investigate the therapeutic effect of hypothermia on intracranial hypertension after traumatic brain injury. The primary outcome measure was the Extended Glasgow Outcome Scale score at six months.

Patients admitted to the ICU after a primary closed traumatic brain injury, with an abnormal CT brain scan, an elevated intracranial pressure (> 20 mmHg for at least 5 minutes) after optimised ventilation and sedation, and who were within 10 days of initial injury, were eligible for randomisation. Exclusion criteria included: hypothermia with a temperature of 34 °C or less at ICU admission; use of therapeutic hypothermia; or prior use of a barbiturate infusion. Randomisation was performed centrally and stratified by site, age, presenting Glasgow Coma Scale motor score, time from injury, and pupillary response.

Patients were initially treated with stage one management. If intracranial hypertension persisted, patients were randomised to either standard stage two management or

Stage 1 Management	
• sedation • intubation and ventilation • elevation of the head of the bed • maintenance of a mean arterial pressure > 80 mmHg • ventriculostomy and surgical removal of space occupying lesions (if required)	
Stage 2 Management	
Standard Management	***Intervention***
• mannitol • hypertonic saline • maintenance of a cerebral perfusion pressure > 60 mmHg	• Therapeutic hypothermia at 32 °C to 35 °C
Stage 3 Management	
• barbiturate therapy • decompressive craniectomy	

intracranial pressure management with hypothermia. Standard stage two treatments were also allowed in the hypothermic group if necessary, but only after induced hypothermia. Stage three management was introduced if intracranial pressure was not controlled (> 20 mmHg) after stage two management

In the hypothermia group, hypothermia was induced using a bolus of refrigerated 0.9% saline (20 to 30 ml/kg) and subsequently maintained with the cooling technique normally used in each unit. Hypothermia was continued for a minimum of 48 hours. The protocol provided guidance on induction of hypothermia, maintenance and gradual rewarming. Core temperature was sustained between 32 °C and 35 °C to maintain ICP below 20 mmHg. Failure to achieve this goal resulted in the introduction of further stage two therapies.

The primary outcome measure was the score on the Extended Glasgow Outcome Scale (GOS-E) at 6 months after injury. Secondary outcomes were 6-month mortality, lack of intracranial pressure control (failure of all stage 2 therapies to control intracranial pressure to ≤ 20 mmHg), incidence of pneumonia up to 7 days after randomisation, length of ICU stay, and grade on the modified Oxford Handicap Scale (MOHS). Data were also collected on serious adverse events; specifically bleeding, cardiovascular instability, thermal burns, and a cerebral perfusion pressure of less than 50 mmHg.

After a pilot phase the sample size was reduced from 1,800 patients to 600 patients. This resulted in an 80% power to detect a rate of unfavorable outcome (GOS-E score of 1 to 4) that was 9%ial lower with hypothermia than with standard care (51% vs. 60%), at a two-sided 5% significance level. The sample size reduction was justified as the patients enrolled had proven brain swelling and the pilot showed enhanced cooling was achievable.

A total of 2,498 patients were assessed, and 387 patients at 47 centers in 18 countries underwent randomisation. The main reasons for exclusion were controlled intracranial pressure (41%), unsurvivable injury (8%) and therapeutic hypothermia (6%). The trial was stopped prematurely after the steering committee concluded there was a signal of harm from the treatment. When the trial was stopped 195 patients had been randomized to the hypothermia group and 192 to the control group. One patient was withdrawn. Baseline characteristics of the two groups were similar; in particular, age, the initial GCS, papillary responses and the type of injury.

During the intervention, the mean daily intracranial pressure was similar in the two groups. Core temperature was significantly lower in the hypothermia group (difference −2.14 °C; 95% CI, −2.34 to −1.94; P < 0.001) during the first 4 days. During this time there were fewer first occurrences of failure of stage 2 therapy to control intracranial pressure in the hypothermia group than in the control group (57 vs. 84), which resulted in more

frequent use of stage 3 treatments in the first seven days in the control group (102 of 189 patients [54.0%] vs. 84 of 192 patients [43.8%]). Barbiturate-infusion therapy was used more often in the control group than in the hypothermia group (41 patients vs. 20 patients), but decompressive craniectomy rates were almost identical (27 patients in each group).

For the primary outcome, six months after injury, the distribution of GOS-E scores suggested harm in the hypothermia group (adjusted common OR, 1.53; 95% CI, 1.02 to 2.30; P = 0.04). Favorable outcomes (GOS-E score of 5 to 8, indicating moderate disability or good recovery) occurred in 49 of 191 patients (25.7%) in the hypothermia group and in 69 of 189 patients (36.5%) in the control group (P = 0.03). The risk of death (HR, 1.45; 95% CI, 1.01 to 2.10; P = 0.047) favored the control group. Subgroup analysis showed no significant interactions. There were more episodes of adverse events in the hypothermia group (33 events vs. 10 events).

Critique

Traumatic brain injury (TBI) is a common and serious worldwide problem. Animal models have advanced the understanding of the complex pathophysiological changes associated with TBI and identified potential therapeutic interventions.[1,2] Despite a better understanding of brain injury and successful interventions reported in pre-clinical models, there is little clinical data to support many of the treatments currently used.[3-5] Therapeutic hypothermia has been previously investigated[6] and there are several mechanisms through which cooling may reduce swelling following brain injury, including reduction of proinflammatory cytokine levels, decreased cellular inflammatory response, and stabilisation of the blood–brain barrier. However, despite multiple clinical trials of hypothermia treatment in patients with severe brain injury, results have been inconsistent, perhaps due to the heterogeneity of trial design.[7] Despite a paucity of beneficial outcome evidence, hypothermia is still used as treatment and rescue therapy. However, after recent questioning of the true value of hypothermia in cardiac arrest patients, establishing whether applying hypothermia in traumatic brain injury patients requires clarification.[8]

This trial attempts to address the use of hypothermia alongside the use of osmotic agents, but only after the establishment of the essential, initial management steps of mechanical ventilation, adequate sedation and head of the bed elevation. There are many positives aspects in the conduct of this trial. The protocol was previously published and the trial design was informed by pilot data which allowed for a reduction in patient numbers while maintaining statistical power. The inclusion criteria guaranteed a population with established brain injury and the randomisation process produced balanced study groups. This was a pragmatic trial and the management of brain injury followed best practice guidelines in centres with experience in head injury management, which adds to the generalisation of the results. Furthermore, the intervention

established a cooling protocol with ICP management, but with equipment already in use and familiar to each ICU. The rewarming strategy was controlled at 0.25 °C per hour, reducing the risk of potential harm with rapid warming.[9] The trial endpoints were clinically relevant, and although a composite end point of death and severe disability was used, this meant the analysis would not establish a positive outcome which reduced mortality at the expense of severe disability. Finally, the trial had a interim safety analysis, which ultimately resulted in early termination. This does mean that the trial risks bias, however, the remaining results collected did not show regression toward the mean, suggesting this was not the case.

There are also some interesting discussion points with this trial. As previously mentioned, the inclusion criteria meant patients had evidence of brain injury, however, the elevated ICP criteria resulted in many patients who were intubated and ventilated being excluded. The inclusion criteria were modified to include patients up to 10 days after injury, to allow adequate time for brain swelling and therefore capture all severe brain injuries. However, simply randomising all TBI patients with an ICP greater than 20 mmHg for 5 minutes after stage 1 therapy, may not represent those with truly severe TBI. The motor GCS and 20 mmHg ICP alone do not necessarily equate to severe TBI. In this trial, the majority of patients were at least flexing normally to pain and had bilateral pupils reactive to light. Perhaps ICP is the not an adequate measure of injury severity and consequently not the correct therapeutic target.

The ability of therapeutic hypothermia to normalise ICP in this trial did not translate to improved outcomes. The use of ICP has already been questioned.[10] In this study, patients suffered from heterogeneous brain injuries. A further reason for failure of the intervention may have been this was the wrong patient population. There is evidence early hypothermia may improve outcomes in patients undergoing surgical decompression for focal insults but does not improve outcomes in patients with diffuse brain injury.[11] These findings suggest specific therapeutic approaches may be required for specific types of severe TBI. The Hypothermia for Patients requiring Evacuation of Subdural Hematoma (HOPES) trial may address some of these questions (NCT02064959)

The intervention should also be examined. Previous studies targeting hypothermia during the peak timing of raised intracranial pressure (3–5 days), or until intracranial hypertension resolved, have mainly produced positive outcomes.[12-16] However, when patients were treated for predefined periods of time, the positive results have not been emulated.[17-19] In the Eurotherm study, the intervention was targeted, but as the majority of patients were randomised after 12 hours, perhaps the intervention was not early enough. The delivery of the intervention, and in particular, the stage two therapies should also be examined. The trial did not record the use of stage two therapies in the groups. It is unknown which additional stage two treatments were required. Therefore, the question arises was this a trial of primarily osmolar agent therapy against

hypothermia or a combination? Perhaps the use of other Stage 2 therapies caused the harm / benefit effect seen in this trial. The timing of the hypothermia before osmolar agents is also perhaps different to how hypothermia is used in some units.

As a final thought, perhaps the functional outcome measures used in TBI need to be reassessed, and other potentially more sensitive outcome measures require development in the future.

Where it sits in the body of evidence

- The effects of moderate hypothermia and normothermia were evaluated in a single-centre trial in 82 patients with severe closed head injuries (a score of 3 to 7 on the Glasgow Coma Scale) investigated.[18] The patients assigned to hypothermia were cooled to 33°C a mean of 10 hours after injury, and temperature maintained for 24 hours with subsequent rewarming. The patients were evaluated at 3, 6, and 12 months with the use of the Glasgow Outcome Scale. At 12 months, 62% of patients in the hypothermia group and 38% of those in the normothermia group had good outcomes (moderate, mild, or no disabilities). The adjusted risk ratio for a bad outcome in the hypothermia group was 0.5 (95% CI, 0.2 to 1.2). Hypothermia did not improve the outcomes in the patients with coma scores of 3 or 4 on admission.

- In a small study investigating the long term effects of hypothermia in TBI, 43 patients assigned to a mild hypothermia group, were cooled to between 33 °C and 35 °C a mean of 15 hours after injury and kept this temperature for 3 to 14 days.[12] Rewarming commenced when the individual patient's ICP returned to the normal. Body temperatures in 44 patients assigned to a normothermia group were maintained at 37 °C to 38 °C. Each patient's outcome was evaluated 1 year later by using the Glasgow Outcome Scale. One year after TBI, the mortality rate was 25.58% (11 of 43 patients) and the rate of favourable outcome (good recovery or moderate disability) was 46.51% (20 of 43 patients) in the mild hypothermia group. In the normothermia group, the mortality rate was 45.45% (20 of 44 patients) and the rate of favourable outcome was 27.27% (12 of 44 patients) ($P < 0.05$). Induced mild hypothermia also markedly reduced ICP ($P < 0.01$) and inhibited hyperglycemia ($P < 0.05$).

- In a similar sized study to Eurotherm, 392 patients, aged 16 to 65, with coma after closed head injury, were randomised to treatment with hypothermia (33 °C), initiated within 6 hours after injury and maintained for 48 hours by means of surface cooling, or normothermia.[17] The primary outcome measure was functional status at six months. The mean (± SD) time from injury to randomisation was 4.3 ± 1.1 hours in the hypothermia group and 4.1 ± 1.2 hours in the normothermia group. The mean time from injury to the achievement of the target temperature of 33 °C in the hypothermia group was 8.4 ± 3.0 hours. The outcome was poor (defined as severe disability, a vegetative state, or death) in 57% of patients in both groups. Mortality was 28% in the

hypothermia group and 27% in the normothermia group (P=0.79). The patients in the hypothermia group had more hospital days with complications. Fewer patients in the hypothermia group had raised intracranial pressure than in the normothermia group.

- The National Acute Brain Injury Study: Hypothermia II (NABIS: H II) was a randomised, multi-centre trial of patients with severe brain injury who were enrolled within 2·5 hours of injury.[11] Patients with non-penetrating brain injury who were 16 to 45 years old and not responsive to instructions were randomly assigned to hypothermia or normothermia. Patients randomly assigned to hypothermia were cooled to 35 °C until their trauma assessment was completed. Patients who had none of a second set of exclusion criteria were either cooled to 33 °C for 48 hours, and then gradually rewarmed, or treated at normothermia. The primary outcome was the Glasgow Outcome Scale score at 6 months. Two hundred and thirty-two patients were randomised a mean of 1·6 hours (SD 0·5) after injury: 119 to hypothermia and 113 to normothermia. Ninety-seven patients (52 in the hypothermia group and 45 in the normothermia group) did not meet any of the second set of exclusion criteria. The mean time to 35 °C for the 52 patients in the hypothermia group was 2·6 hours (SD 1·2) and to 33 °C was 4·4 hours (1·5). Outcome was poor (severe disability, vegetative state, or death) in 31 of 52 patients in the hypothermia group and 25 of 56 in the normothermia group (RR, 1·08; 95% CI, 0·76 to 1·53; P = 0·67). Twelve patients in the hypothermia group died compared with 8 in the normothermia group (RR 1·30, 95% CI 0·58-2·52; p=0·52).

- In the post hoc B-HYPO study, patient data was evaluated based on the severity of trauma as AIS (Abbreviated Injury Scale) 3-4 or AIS 5 and compared Glasgow Outcome Scale score and mortality at 6 months.[20] One hundred and twenty-nine patients were evaluated, 47 and 31 patients with AIS 3-4 and 36 and 15 patients with AIS 5 were allocated to the mild therapeutic hypothermia (MTH) and fever control groups respectively. The fever control group demonstrated a significant reduction of TBI-related mortality compared with the MTH group (9.7% vs. 34.0%, P = 0.02) and an increase of favourable neurological outcomes (64.5% vs. 51.1%, P = 0.26) in patients with AIS 3-4, although the latter was not statistically significant. There was no difference in mortality or favourable outcome in patients with AIS 5. Fever control may be considered instead of MTH in patients with TBI (AIS 3-4).

- In a multi-centre trial, patients with severe TBI (GCS 4-8) were randomly assigned (2:1 allocation ratio) to either therapeutic hypothermia (32-34 °C, n = 98) or fever control (35.5 °C to 37 °C, n = 50).[21] Patients with therapeutic hypothermia were cooled as soon as possible for ≥ 72 hours and rewarmed at a rate of < 1 °C/day. All patients received tight haemodynamic monitoring. The Glasgow Outcome Scale was assessed at 6 months. The overall rates of poor neurological outcomes were 53% and 48% in the therapeutic hypothermia and fever control groups, respectively. There were no

significant differences in the likelihood of poor neurological outcome (RR, 1.24; 95% CI, 0.62 to 2.48; P = 0.597) or mortality (RR, 1.82; 95% CI, 0.82 - 4.03, P = 0.180) between the two groups.

- Eighty patients with severe TBI after unilateral craniotomy were randomized into a therapeutic hypothermia group, with brain temperature maintained at 33 °C to 35 °C for 4 days, and a normothermia control group.[14] Vital signs, intracranial pressure, serum superoxide dismutase level, Glasgow Outcome Scale scores, and complications were prospectively analyzed. The mean intracranial pressure values of the therapeutic hypothermia group at 24, 48, and 72 hours after injury were lower than those of the control group (23.49 ± 2.38, 24.68 ± 1.71, and 22.51 ± 2.44 vs 25.87 ± 2.18, 25.90 ± 1.86, and 24.57 ± 3.95 mmHg; P =0.001, 0.001, and 0.003, respectively). The percentage of favourable neurological outcome 1 year after injury was 70.0% and 47.5%, respectively (P =0 .041). Complications were more common (57.5%) in the therapeutic hypothermia group than in the control group (32.5%)(P = 0.025).

- In a before and after retrospective analysis, the ICP and biochemical parameters in 30 patients treated with hypothermia at 35 °C (January 2000 to June 2005) were compared with 31 patients treated with hypothermia at 33 °C (July 1994 to December 1999).[22] The mean temperature during hypothermia was 35.1 °C ± 0.7 °C in the 35 °C hypothermia group and 33.4 °C ± 0.8 °C in the 33 °C hypothermia group. Mean ICP was controlled under 20 mmHg during hypothermia in both groups. The incidence of intracranial hypertension and low cerebral perfusion pressure did not differ. The 35 °C hypothermia patients exhibited a significant improvement in the decline of serum potassium concentrations during hypothermia and in the increment of C-reactive protein after rewarming.

- Jiang and colleagues completed a multi centre trial examining the effects of long-term mild hypothermia, lasting 5 ± 1.3 day (n = 108), with short-term mild hypothermia, lasting 2 ± 0.6 days (n = 107), in 215 patients with cerebral contusion and intracranial hypertension.[13] The patients were aged 18 to 45 years old and had an admission Glasgow Coma Scale ≤ 8 within 4 hours of injury. At 6-month follow-up, in the long-term mild hypothermia group, 47 cases had a favourable outcome (43.5%), and 61 cases had an unfavourable outcome (56.5%). In the short-term mild hypothermia group, only 31 cases had a favourable outcome (29.0%), with the remaining 76 cases having an unfavourable outcome (71.0%) (P < 0.05). The intracranial pressure significantly rebounded after rewarming in the short-term mild hypothermia group, but not in the long-term mild hypothermia (P < 0.05).

- Polderman and colleagues performed a prospective clinical trial in 136 patients with a GCS ≤ 8 on admission, in whom ICP remained above 20 mmHg in spite of therapy according to a step-up protocol.[23] Patients who responded to the last step of the

protocol, which was barbiturate coma (n = 72), were compared with those who did not and were further treated with therapeutic hypothermia at 32 °C- to 34 °C (n = 64). The predicted mortality was 86% for the hypothermia group and 80% for controls (P < 0.01). Actual mortality rates were lower and significantly different; 62% versus 72%, respectively (P < 0.05). The number of patients with good neurological outcome was also higher in the hypothermia group, 15.7% versus 9.7%, respectively (p<0.02).

- Shiozaki and colleagues evaluated the efficacy of moderate hypothermia (31 °C) in 22 patients with severe head injury and intracranial hypertension (> 40 mmHg) refractory to mild hypothermia (34 °C). In 19 of 22 patients (86%), raised ICP remained refractory to further hypothermia. In the remaining three patients, ICP was maintained below 40 mm Hg with the introduction of moderate hypothermia; however, these three patients died of multiple organ failure.[16]

- Ninety-one patients with severe TBI, in whom ICP could be maintained below 25 mmHg with conventional therapies, were randomised to receive either mild hypothermia at 34 °C (HT group, n = 45) or normothermia at 37 °C (NT group, n = 46).[19] Patients in the HT group were managed at 34 °C for 48 hours, followed by rewarming at 1 °C per day for 3 days; whereas patients in the NT group were exposed to normothermia (37 °C) for 5 days. During the initial 2 weeks postinjury, the incidences of pneumonia, meningitis, leukocytopaenia, thrombocytopenia, hypernatraemia, hypokalaemia, and hyperamylasaemia were significantly higher in the HT than in the NT group (P < 0.05).

- In a post hoc analysis of two TBI hypothermia trials, the effects of hypothermia on patients with evacuated haematomas were examined.[24] Forty-six patients who reached 35 °C within 1.5 hours of commencement of surgery showed a significantly reduced rate of poor outcomes (41%) compared with the 94 patients treated with hypothermia who did not reach 35 °C within that time and also with patients treated at normothermia (62%) (P = 0.009).

- The international Targeted Temperature Management (TTM) trial, randomised 950 unconscious adults after out-of-hospital cardiac arrest of presumed cardiac cause to TTM at either 33 °C or 36 °C.[8] The primary outcome was all-cause mortality at the end of the trial. Secondary outcomes included a composite of poor neurological function or death at 180 days, as evaluated with the Cerebral Performance Category (CPC) scale and the modified Rankin scale. In total, 939 patients were included in the primary analysis. At the end of the trial, 50% of the patients in the 33 °C group (235 of 473 patients) had died, as compared with 48% of the patients in the 36 °C group (225 of 466 patients) (HR with a temperature of 33 °C, 1.06; 95% CI, 0.89 to 1.28; P = 0.51). At the 180-day follow-up, 54% of the patients in the 33°C group had died or had poor neurological function, as compared with 52% of patients in the 36 °C group (RR, 1.02; 95% CI, 0.88 to 1.16; P = 0.78). In the analysis using the modified Rankin scale, the rate was 52% in both groups (RR, 1.01; 95% CI, 0.89 to 1.14; P = 0.87). The results of

analyses adjusted for known prognostic factors were similar.

- In a multi-centre, international trial, children with severe traumatic brain injury were randomised to either hypothermia (32.5 °C for 24 hours) initiated within 8 hours after injury or to normothermia (37.0 °C).[25] The primary outcome was the proportion of children with an unfavourable outcome (i.e., severe disability, persistent vegetative state, or death), as assessed on the basis of the Pediatric Cerebral Performance Category score at 6 months. A total of 225 children were recruited. The mean temperatures achieved in the two groups were 33.1+/-1.2 °C and 36.9+/-0.5 °C, respectively. At 6 months, 31% of the patients in the hypothermia group, as compared with 22% of the patients in the normothermia group, had an unfavorable outcome (RR, 1.41; 95% CI, 0.89 to 2.22; P = 0.14). There were 23 deaths (21%) in the hypothermia group and 14 deaths (12%) in the normothermia group (RR, 1.40; 95% CI, 0.90 to 2.27; P = 0.06). More patients were hypotensive (P = 0.047) and more vasoactive agents were administered (P < 0.001) in the hypothermia group during the rewarming period than in the normothermia group.

- In a small, multi-centre, international trial, children with early (within 6 hours), severe traumatic brain injury were randomised to either hypothermia (rapidly cooled to 32 °C to 33 °C, and maintained for 48 to 72 hours, then rewarmed by 0·5 °C to 1·0 °C every 12 to 24 hours) or normothermia (maintained at 36·5 °C to 37·5 °C).[26] The study was terminated early for futility after an interim data analysis on 77 patients. There was no difference in the primary outcome of 3-mortality, 15% [6/39] in the hypothermia group vs 5% (2/38) in the normothermia group; (P = 0·15). There was also no difference in the incidence of poor outcomes between groups; hypothermia group 42% vs normothermia group 47%.

- Very recently, Beca and colleagues reported a multi-centre phase II trial conducted in children aged 1-15 years old with early severe traumatic brain injury.[27] Fifty-five children within 6 hours of injury were randomised to hypothermia (temperature of 32 °C to 33 °C) for 72 hours followed by slow rewarming at a rate compatible with maintaining intracranial pressure and cerebral perfusion pressure, or to strict normothermia. Rewarming took a median of 21.5 hours (16 to 35 hours). There was no difference in outcomes 12 months after injury, or in acute complications, including infections, bleeding, and arrhythmias.

Should we implement this into our practice?
No. Therapeutic hypothermia should not be used routinely for stage two management of traumatic brain injury.

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The EPO-TBI Trial

Nichol A, French C, Little L, Haddad S, Presneill J, Arabi Y, et al. Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. Lancet 2015;386(10012):2444-2506

Study Synopsis

EPO-TBI was an international double-blind, placebo-controlled trial which randomised 606 patients with early moderate to severe traumatic brain injury (TBI) to erythropoietin (EPO)(40 000 units subcutaneously) or placebo (0·9% saline subcutaneously) once per week for a maximum of three doses. In animal models, EPO has pleiotropic neurocytoprotective effects, including being anti-excitotoxic, antioxidant, anti-edematous, and anti-inflammatory.[1] Additionally, EPO crosses the blood-brain barrier. However, EPO stimulates erythropoiesis, risking thrombotic complications, especially in the critically ill who are already vulnerable to this.

Patients within 24 hours of TBI were assigned by a concealed web-based computer-generated randomisation schedule, which included stratification by severity of TBI (moderate vs severe) and participating site. The investigative team, patients and patients' relatives were blinded to the intervention, which was only known to the site pharmacists, the site dosing nurses, and pharmacists at the central pharmacy in France.

The primary outcome, assessed at 6 months by a modified intention-to-treat analysis, was improvement in patients' neurological status, summarised as a reduction in the proportion of patients with a Extended Glasgow Outcome Scale (GOS-E) of 1–4 (death, vegetative state, and severe disability). Two preplanned interim analyses were performed after 202 and 404 participants were enrolled, respectively. A planned sample size of 574 evaluable patients had greater than 90% power to detect a 28% relative risk reduction (from 50% to 36%) and roughly 80% power to detect a 24% relative risk reduction (from 50% to 38%), both at the 5% significance level. This sample size was increased from 574 to 606 patients to allow for a combined withdrawal and loss to follow-up of 5%.

Patients received either epoetin alfa 40 000 U (Eprex Janssen-Cilag Pty Ltd, Titusville, NJ, USA) or placebo (0·9% saline) as a subcutaneous injection. The first dose was administered within 24 h of TBI and then weekly for a maximum of three doses, as long as the patient remained in ICU, their haemoglobin concentration was lower than 120 g/L, and they had not met other withholding criteria. Screening ultrasound examinations of the lower extremities were done in a standardised manner, within 48 hours of the administration of the first dose of trial drug and then twice weekly, for up to 3 weeks or until discharge .

3,384 patients were screened and 606 randomised, 308 to EPO and 298 to placebo. Both groups were well matched at baseline. Ten patients were lost to follow up at 6 months.

EPO did not reduce the proportion of patients with a GOS-E level of 1–4 compared with placebo; 44% (134/302) vs 45% (132/294) , respectively; (RR, 0·99; 95% CI, 0·83 to 1·18; P = 0·90). There was no difference in 6-month mortality, (EPO, 11% vs placebo, 16%; RR, 0·68; 95% CI, 0·44 to 1·03; P = 0·07) or increase in the occurrence of deep venous thrombosis of the lower limbs (16% vs 18%, respectively; RR, 0·87, 95% CI 0·61 to 1·24; P = 0·44).

Critique

EPO-TBI was a large, robust randomised controlled trial evaluating both the efficacy and safety of EPO in moderate to severe TBI. The trial has many strengths; a sound biological rationale; a robust randomisation process, successfully resulting in balanced groups at baseline; blinding of investigators and assessors; appropriate stratification for identification of important group effects; and a focus on safety, including routine screening for lower limb deep venous thrombosis.

There are few apparent weaknesses in the trial design. Firstly, In comparison with the recent EPO Severe TBI Trial by Robertson, EPO-TBI used a much larger dose of the intervention (40 000 units versus 500 U/kg).[2] This large dose of EPO was used at a once-weekly dosing frequency. Given the lack of effect of EPO on the incidence of deep venous thrombosis, it can be speculated more frequent administration, and thus increasing the delivered dose, could have proven beneficial. Experimental animal models used doses of EPO ten times that of EPO-TBI.[1] Consistent with this, just 26% of patients received all three doses of EPO. If EPO was effective, but under-dosed, then a smaller effect may exist. Unfortunately, the power calculation used a relative risk reduction of approximately one-quarter, which appears optimistic. However, the numerical similarity of results from both groups do not suggest this trial is underpowered for a smaller effect.

Secondly, although administration of EPO within 24 hours of the onset of TBI is laudable, it may already be too late and minimise its effective, with animal work suggesting an earlier time point of administration may be superior. It is for this reason, the EPO Stroke Trial administered the trial drug within 6 hours to maximise this effect.

Thirdly, syndromic research in critical care has largely proven an unrewarding field of investigation. The heterogeneity of TBI, including extra-axial versus parenchymal haemhorrhage, diffuse versus focal insults and the wide age range affected, likely make it difficult to identify a single intervention which may alter such a range of pathologies.

A planned sensitivity analysis, adjusting for known prognostic covariates at admission,

returned a significantly lower mortality in patients without a mass lesion in the EPO group (adjusted HR, 0·62; 95% CI, 0·39 to 0·97; P = 0·04), but no difference in dichotomised GOS-E scores. This result is likely to encourage further work into the use of EPO in trauma and TBI, but at present should be considered hypothesis-generating only.

Where it sits in the body of evidence

- Robertson and colleagues completed a small 2 x 2 factorial trial (EPO Severe TBI) of 200 patients with closed TBI in two American trauma centres.[2] Patients were randomly assigned to receive EPO (n = 102) or placebo (n = 98), and to a haemoglobin transfusion threshold of 7 g/dL (n = 99) or 10 g/dL (n = 101). 500 IU/kg of EPO or placebo was administered within 6 hours of injury for all patients, as well as on days 2 and 3 (for the first 76 patients only, due to a protocol change for safety reasons), followed by two further once weekly doses if the haemoglobin level remained under 12 g/dL. There was no interaction between EPO and haemoglobin transfusion threshold. EPO administration did not result in more favourable outcomes: placebo group, 38.2%; (95% CI, 28.1% to 49.1%) versus first dosing regimen EPO group, 48.6%; (95% CI, 31.4% to 66.0%; P = 0.13); and second dosing regimen, 29.8%; (95% CI, 18.4% to 43.4%, P < 0.001). There was also no difference in rates of favourable outcomes between the transfusion threshold groups; 7 g/dL (42.5%) and 10 g/dL (33.0%) (95% CI for the difference, −0.06 to 0.25; P = 0.28). There was a lower incidence of thromboembolic events for the transfusion threshold of 7 g/dL; (8.1% vs 21.8%; OR, 0.32; 95% CI, 0.12 to 0.79, P = 0.009).

- Corwin and colleagues randomised a mixed population of 1,460 critically ill patients, 48 to 96 hours after admission to the ICU, to either subcutaneous EPO (40,000 U) or placebo, which was administered on the day of admission and weekly thereafter for a maximum of 3 weeks.[3] There were no significant difference between the groups in the percentage of patients who received a red-cell transfusion (EPO, 46.0% vs placebo, 48.3%; RR, 0.95; 95% CI, 0.85 to 1.06; P = 0.34). EPO administration resulted in a significantly lower day 29 mortality (8.5% vs. 11.4%, P=0.02), including in the trauma subgroup, (3.5% vs 6.6%, P = 0.04). Statistical significance was lost at day 140; for the entire cohort,14.2% vs 16.8%, P=0.08; and for the trauma subgroup, 6.0% vs. 9.2%, P=0.08.

- The double blind EPO Stroke Trial randomised 522 patients with middle cerebral artery territory ischaemic stroke to 40 000 U EPO intravenously or placebo, administered within 6 hours of stroke onset, and again at 24 and 48 hours.[4] Four hundred and sixty patients were treated per protocol. Systemic thrombolysis with recombinant tissue plasminogen activator was allowed, stratified for and received by 63% of the study cohort. Not only did EPO administration not result in improved functional outcomes, but it resulted in increased mortality; 16.4% (42 of 256) vs 9.0% (24 of 266) (OR, 1.98; 95% CI, 1.16 to 3.38; P = 0.01).

Should we implement this into our practice?
No, the results of this trial do not support the use of erythropoietin for the management of traumatic brain injury. Further research in this field is likely.

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Lacroix J, Hébert PC, Fergusson DA, Tinmouth A, Cook DJ, Marshall JC, et al. Age of Transfused Blood in Critically Ill Adults. New England Journal of Medicine. 2015 Apr 9;372(15):1410–8.

Study synopsis

This multi-centre, randomised, blinded trial, carried out in Canada and Europe, examined the effects of the age of transfused red blood cells in critically ill patients. It hypothesised the administration of fresh red blood cells (RBCs), stored for less than 8 days, would result in a lower mortality than standard-issue RBCs. The primary outcome measure was 90-day mortality.

Critically ill patients due to receive a RBC transfusion for the first time within the initial seven days of their ICU stay were eligible. Patients were required to be aged 18 and over and expected to require invasive or non-invasive ventilation for a minimum of 48 hours.

The intervention consisted of transfusion of RBCs less than 8 days old (fresh blood group) and was compared with the oldest compatible RBC unit available in the blood bank (standard blood group). The RBCs were leukoreduced and stored in saline–adenine–glucose–mannitol solutions. In instances where there were no compatible RBC less than 8 days old, patients were transfused with the youngest compatible RBCs. This intervention was continued until hospital discharge, death or up to 90 days post randomisation (this was beyond the primary end point of death at 90 days). To ensure blinding of the treating clinicians, the collection and expiration dates on each unit of RBCs was obscured using an opaque sticker. The decision to transfuse was at the discretion of the treating physicians.

Assuming a baseline mortality of 25%, a total sample of 2,266 patients were needed to have a 90% power to detect an absolute difference in mortality of 5%. An intention-to-treat analysis was carried out, as was a per-protocol analysis (which included patients who had received blood older then 8 days old where fresher blood was not available) and a sensitivity analysis (which compared only those who received RBCs fresher than 8 days with blood that was older then 7 days).

19,196 patients were screened between 2009 and 2014. A total of 2,510 patients were recruited from tertiary level ICUs. 3.2% of patients were lost to follow up, leaving 2,430 patients available for the primary analysis. The groups were well balanced at baseline. The total number of RBC units transfused was 5,198 in the fresh-blood group and 5,210 in the standard-blood group. The mean haemoglobin prior to first transfusion was 7.69 ± 1.28 g/dL in the fresh-blood group and 7.64 ± 1.09 g/dL in the standard-blood group (P = 0.27).

There was good separation between groups with the mean age of blood 6.1 ± 4.9 days in the fresh-blood group versus 22.0 ± 8.4 days in the standard-blood group (P < 0.001). All patients in the standard blood group received the oldest compatible unit of RBC. 84% of patients in the fresh blood group received only blood less than 8 days old, with 90.9% of all transfused RBCs in the fresh blood group being less than 8 days old.

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). There was no difference in mortality at any time point. Pre-specified subgroup analyses demonstrated no difference in mortality on the basis of age, number of units transfused, APACHE II score or admission category. Again, per-protocol and sensitivity analyses showed no mortality differences between the two groups. There was no difference in time to death.

Similarly, there was no difference in any of the secondary outcomes including incidence of multiple organ dysfunction syndrome, ARDS, cardiac ischaemia, thromboembolic events, duration of organ support or length of ICU stay.

Critique

This was a large well conducted trial into a common and important issue in critical care . Previous retrospective studies suggested an increase in mortality with increasing age of blood.[1] However, a meta-analysis of small RCTs and observational studies suggest there was a reduction in mortality with transfusion of old blood.[2] Equipoise was created by this conflicting evidence coupled with the fact that standard care in transfusion medicine is to administer the oldest unit of RBCs in the blood bank. In addition, there is biological plausibility that either fresh RBCs may be better (due to increased oxygen carrying capacity) or old RBCs may be better (due to less immunosuppression).

The power calculations in this study assumed a 25% mortality and a 5% difference between groups. The observed mortality was 37% and the mortality difference between groups was 1.7% in favour of standard-blood group. It is conceivable this study missed a very small treatment effect but this is unlikely ever to be answered by a randomised controlled trial.

The investigators question whether there may be a subset of ICU patients that benefit from fresh blood or can be harmed by very old blood. There is a theoretical risk that patients with sepsis may be harmed by old blood due to the increase in free iron available which induces inflammation and may be pro-bacterial.[3] To counter this, the absence of treatment effect was seen across multiple subgroups including patients of different age, APACHE II score and admission criteria. Indeed, there was no difference in nosocomial infections between the two groups. This, in conjunction with the mixed ICU population, strengthens the argument that the results of this trial are applicable to a

wide range of ICU patients. This trial used leukoreduced RBCs suspended in saline–adenine–glucose–mannitol solutions which may limit its generalisability to regions where different storage solutions are used.

ABLE was published in the same year as two other trials looking at the effect of duration of storage of RBCs on outcomes. The RECESS trial examined the effect of RBC storage duration on Multiple Organ Dysfunction Scores in patients following complex cardiac surgery and reported no difference in outcomes.[4] A study by Fergusson and colleagues randomised low birth weigh premature infants to fresh blood or standard issue blood, and again found no difference in outcomes.[5] Hence, the results of the ABLE trial are consistent with other contemporary age of red cell transfusion studies in differing populations.

There was good separation between the two groups in terms of age of transfused RBCs (6.1± 4.9 days in the fresh-blood group versus 22.0 ± 8.4 days in the standard-blood group ($P < 0.001$)), but it is unclear whether there is a point beyond which older blood becomes harmful. A large Scandinavian cohort study, involving 404,959 transfusion episodes, demonstrated a 5% increase in mortality in patients who received RBCs stored for between 30 - 42 days. This effect persisted from seven days to two years.[1] The ABLE investigators acknowledge this is a trial that answers the question “is fresh blood good?” rather than “is old blood bad?”.

The number of transfused units of RBCs per patient was low (mean 4.3 per patient). This raises the question whether the lack of difference may have been due to an inadequate “dose” of RBCs. The haemoglobin level at first transfusion averaged 7.6 g/dL, indicating most clinicians were using a restrictive transfusion policy and that the study is reflective of current critical care practice. To answer the question whether patients receiving massive transfusion would benefit from younger blood would require a further trial.

An important distinction should be made when we interpret the results from this trial; we can conclude that there is no benefit in transfusing patients fresh blood (less than 8 days old) but we cannot determine if very old blood is harmful. The RECESS trial, where the age of blood in the longer term storage group was 28.3 ± 6.7 days on average, goes further in answering the question “is old blood harmful?”. However, the RECESS trial used change in Multiple Organ Dysfunction Scores as an outcome measure. In comparison, the much larger ABLE trial used mortality as the primary outcome measure. It is for these reasons the ABLE trial should be considered the best evidence to date on the effect of storage duration of transfused RBCs on patient outcomes.

Where it sits in the body of evidence

- In a paper closely related to the ABLE study; the RECESS study examined the effect of transfusing RBCs stored for 10 days or less (shorter-term storage group) or for 21 days or more (longer-term storage group) in patients 12 years or older undergoing complex cardiac surgery.[4] 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 to 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 1,250 g to receive either RBCs less than 7 days old or standard issue RBCs.[5] 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.

- The landmark TRICC study enrolled 838 critically ill patients and compared a restrictive transfusion strategy (a transfusion trigger of 7 g/dL, with a target maintenance haemoglobin of 7 - 9 g/dL) or a liberal transfusion strategy (a transfusion trigger of 10 g/dL, with a target maintenance haemoglobin of 10 - 12 g/dL).[6] 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 critical ill patients with septic shock.[7] Transfusion thresholds were similar to the TRICC study.[4] There was no difference in the primary endpoint of 90-day mortality; 43.0% of 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 to 1.09, P = 0.44).

- The TITRe2 trial evaluated whether a restrictive transfusion threshold (threshold for transfusion 7.5 g/dL), compared with a liberal transfusion threshold (threshold for transfusion 9 g/dL), would reduce postoperative morbidity and healthcare costs in patients following cardiac surgery.[8] Transfusion rates were much lower in the restrictive transfusion group (53.4% vs 92.2%; RR for transfusion, 0.58; 95% CI, 0.54 to 0.62, P < 0.001). 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 2,007 patients were enrolled. The primary outcome measure occurred in 35.1% of the patients in the restrictive transfusion group and 33.0% of the liberal threshold group (odds ratio, 1.11; 95% CI, 0.91 to 1.34; P

= 0.30). Unexpectedly, there were significantly more deaths in the restrictive transfusion group (4.2% vs. 2.6%; HR, 1.64; 95% CI, 1.00 to 2.67; P=0.045).

- 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.[1]

- Robertson and colleagues conducted a randomised trial using a factorial (2 × 2) design to examine the effect of erythropoietin or placebo and transfusion thresholds of either 7 g/dl or 10 g/dL in patients with traumatic brain injury. None of the four treatment arms created an improvement in Glasgow Outcome Score. Patients assigned to the transfusion threshold of 10 g/dL had a higher incidence of thromboembolic events, 21.8% vs. 8.1% (OR, 0.32; 95% CI, 0.12 to 0.79, P = 0.009).[9]

- A randomised controlled trail involving 606 patients was conducted to examine the role of erythropoietin in patients with traumatic brain injury. There was no difference in extended Glasgow Outcome Score or mortality at 6 months.[10]

Should we implement this into our practice?

Yes. This trial supports our current practice of transfusing the oldest RBC units in blood bank. Crucially, it answers the question "is fresh blood good" rather than "is old blood bad".

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The RECESS Study

Steiner ME, Ness PM, Assmann SF, Triulzi DJ, Sloan SR, Delaney M, et al. Effects of Red-Cell Storage Duration on Patients Undergoing Cardiac Surgery. New England Journal of Medicine. 2015 Apr 9;372(15):1419–29.

Study synopsis

This was a multi-centre, randomised, controlled trial examining the age of transfused red blood cells (RBC) on organ dysfunction following cardiac surgery.

Patients aged 12 or older, weighing at least 40 kg, were eligible if they were undergoing complex cardiac surgery via a median sternotomy and were deemed likely to require RBC transfusion in the intraoperative or postoperative period. Patients aged 18 years and older were only eligible if they had a Transfusion Risk Understanding Scoring Tool (TRUST) score of three or higher (range 0 - 8).

Patients were randomly assigned to receive RBCs stored for 10 days or less (shorter-term storage group) or for 21 days or more (longer-term storage group). The intervention consisted of RBCs that were leukoreduced and this intervention was continued until the first occurrence of either the 28th postoperative day, hospital discharge or death. Patients were only randomised if the transfusion service had enough units of RBCs of either age to meet the preoperative group and cross match request. As the expiration dates on the RBCs provided were not obscured, clinicians were not blinded.

The primary outcome measure was the change in Multiple Organ Dysfunction Score (MODS, range 0 - 24, with higher scores indicating a greater degree of organ dysfunction) at 7 days. Preoperative scores were taken as a baseline. There are six organ components included in the MODS. The highest score from each component during the follow up period was taken to calculate the maximum score. The highest scores from each component could occur on different days.

A 7.3 point standard deviation in change of MODS points at 7 days was assumed. The target was to recruit 1,170 patients in order to achieve a two-sided 95% CI of ± 0.85 MODS points for the between-group difference.

Patients were recruited preoperatively but only analysed of they received RBCs intraoperatively or in the first 96 hours postoperatively. 1,481 patients were randomised, and data were analysed for 1,098 patients. Patients were not analysed for the following reasons; 30 patients did not have surgery, 343 patients did not require RBC transfusion in the first 96 hours, and there was withdrawal of consent in 10 cases. The study was terminated early due to time constraints.

There was no difference in the median number of RBC units transfused (3 in each group). The mean age of RBCs in the shorter-term storage group was 7.8 ± 4.8 days compared to 28.3 ± 6.7 days in the longer-term storage group. Units of the assigned storage duration were administered to 89% of patients in the shorter-term storage group and 87% of patients in the longer- term storage group.

There was no difference in the primary outcome measure of mean change in MODS; an increase of 8.5 and 8.7 points was seen in the shorter-term storage group and longer-term storage group respectively (difference 0.2 MODS points, 95% CI, −0.6 to 0.3; P = 0.44). Similarly there was no difference in the primary outcome measure in a per protocol analysis or when change in MODS was measured only after the administration of RBCs.

There was no difference in the secondary outcome measures of 7-day all cause mortality; 2.8% compared with 2.0%, in the shorter-term storage group and longer-term storage group, respectively (P = 0.43). There was no difference in 28-day mortality (4.4% versus 5.3%, respectively (P = 0.57)). There was no difference in ICU or hospital length of stay.

Critique

This study reinforces the results of other trials into the age of blood.[1,2] Like other studies on this topic, its design means it is better able to answer the question; "is fresher blood good?" than the question "is old blood harmful?". Population based observational data suggests that the use of old blood, which has been stored for between 30 and 42 days, is associated with an increase in mortality.[3] In a retrospective study of 6,002 cardiac surgical patients, patients who had received RBCs that had been stored for greater than 14 days were compared to those who had received RBCs that had been stored for less than 14 days. The transfusion of older blood was associated with an increase in complications, in hospital mortality and death at one year. Increasing age of blood was associated with a linear increase in mortality.[4]

As with the other studies on this topic, the mean number of RBC transfused was low; therefore, the dose of RBCs may not have been enough to yield a difference between the two groups. Observational data from 11,963 patients who underwent coronary artery bypass grafting, 5,184 of whom were transfused in the perioperative period, reported the risk of complications increased with each unit of RBC used.[5]

In designing these trials, the investigators were ethically obliged to create an "old blood" comparator that is in keeping with current clinical practice (typically a blood bank model that is "first in, first out").[1,2] As a consequence of this, transfused RBC units in the comparator group have often been stored for less than 30 - 42 days; the storage time which retrospective data has suggested is harmful.[3,4]

In this study, patients in the longer-term storage group received blood that had been stored for 28.3 ± 6.7 days on average. This was older than the ABLE study, where the mean age of stored blood was 22.0 ± 8.4 days in the "standard-blood group".[1] In this regard, the RECESS trial goes further in answering the question "is old blood harmful?" than previous work. This is partly attributable to the study design whereby patients were only randomised if the blood bank could supply blood products of the appropriate age (132 patients were not randomised for this reason). There was good separation between the two groups with very little overlap. Only 5% of RBCs transfused were in the storage range 11-20 days. For this reason the RECESS trial should be considered important as it reassures us regarding our current transfusion practices.

Due to regulatory requirements, the expiration dates on each unit of RBC were not obscured, meaning that clinicians could not be blinded. The use of change in MODS (an entirely objective scoring system) as an outcome measure should obviate this issue. MODS has previously been compared to SOFA and both showed similar ability to predict mortality in an ICU population.[6] Change in MODS was previously used in a post hoc subgroup analysis of the TRICC trial examining the effect of a restrictive transfusion strategy in patients with cardiovascular disease.[7] Like this trial, the TRICC trial and its subsequent subgroup analysis used the worst laboratory values recoded to calculate the change in MODS.[8] Therefore, change in MODS is a surrogate for mortality and has been validated as an outcome measure. Despite this, its use may produce statistically significant results that lack clinical relevance for patients. An example is seen in this study. The change in total serum bilirubin was higher in the longer-term storage group (26 μmol/L) than the shorter term storage group (14 μmol/L) ($P < 0.01$). It would seem this is unlikely to be clinically significant, a fact which the investigators acknowledge.

In conclusion, the findings of this paper echo that of other recent works, and suggest the age of transfused RBCs is unlikely to contribute to a harmful outcome, at least with RBCs aged less than 30 days. This reassures us that our current transfusion practice is safe.

Where it sits in the body of evidence

- The ABLE trial randomised critically ill patients to receive RBCs less than 8 days old compared with the oldest compatible unit available in the blood bank.[1] 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).

- In a double-blind trial, Fergusson and colleagues randomised 377 premature infants with birth weights less than 1,250 g to receive either RBC less than 7 days old or standard issue RBCs.[2] 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.

- A large Scandinavian cohort study, involving 404,959 transfusion episodes, demonstrated a 5% increase in mortality in patients who received RBCs stored for between 30 - 42 days.[3] This effect persisted from 7 days to two years.

- In a retrospective study of 6,002 cardiac surgical patients, patients who had received RBCs stored for greater than 14 days were compared to those who had received RBCs stored for less than 14 days.[4] The groups were unevenly balanced so logistic regression analysis and propensity score matching were 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 administration of RBCs less than 14 days of age would prevent one additional death for every 28 patients treated.

- 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 RBCs was associated with an increase in mortality.[5] 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 landmark TRICC study enrolled 838 critically ill patients and compared a restrictive transfusion strategy (a transfusion trigger of 7 g/dL, with a target maintenance haemoglobin of 7 - 9 g/dL) with a liberal transfusion strategy (a transfusion trigger of 10 g/dL, with a target maintenance haemoglobin of 10 - 12 g/dL).[8] 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 critical ill patients with septic shock.[9] Transfusion thresholds were similar to the TRICC study.[8] There was no difference in the primary endpoint of 90-day mortality; 43.0% of 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 to 1.09; P = 0.44).

- The TITRe2 trial evaluated whether a restrictive transfusion threshold (threshold for transfusion 7.5 g/dL), compared with a liberal transfusion threshold (threshold for transfusion 9 g/dL), would reduce postoperative morbidity and healthcare costs in patients following cardiac surgery.[10] Transfusion rates were much lower in the restrictive transfusion group (53.4% vs 92.2%; RR for transfusion, 0.58; 95% CI, 0.54 to

0.62, P < 0.001). 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 2,007 patients were enrolled. The primary outcome measure occurred in 35.1% of the patients in the restrictive transfusion group and 33.0% of the liberal threshold group (odds ratio, 1.11; 95% CI, 0.91 to 1.34; P = 0.30). Unexpectedly, there were significantly more deaths in the restrictive transfusion group (4.2% vs. 2.6%; HR, 1.64; 95% CI, 1.00 to 2.67; P=0.045).

Should we implement this into our practice?
Yes. This trial supports our current practice of transfusion. Its results are consistent with the other randomised age of blood transfusion trials.

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The TITRe2 Trial

Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, et al. Liberal or Restrictive Transfusion after Cardiac Surgery. New England Journal of Medicine. 2015 Mar 12;372(11):997–1008.

Study synopsis

This multi-centre, parallel-group, randomised controlled trial compared whether restrictive or liberal thresholds for red blood cell (RBC) transfusion after cardiac surgery affected post operative morbidity. Patients were eligible if they were 16 years or older, undergoing non emergency cardiac surgery and had a post operative haemoglobin below 9 g/dL or their haematocrit fell below 27%. Patients were randomly assigned to a transfusion threshold of < 7.5 g/dL (restrictive-threshold group) or 9 g/dL (liberal-threshold group). Treating clinicians were not blinded. Physicians could contravene the assigned transfusion threshold temporarily or discontinue adherence to the transfusion threshold completely (these acts did not constitute withdrawal from the trial).

The primary outcome measure was a composite of serious infection (sepsis or wound infection) or an ischaemic event (permanent stroke, myocardial infarction, infarction of the gut, or acute kidney injury) within the three months of randomisation. Health care costs (excluding the cost of the original surgery) were calculated. The authors assumed the rate of the primary outcome measure to be 11% in the restrictive-threshold group and 17% in the liberal-threshold group. Based on this, a sample size of 1,468 was required to achieve 90% power to detect this difference, at a 5% level of significance. It was planned to recruit 2,000 patients to account for non-adherence.

RBCs were to be transfused within 24 hours of meeting the transfusion threshold. Non-adherence included RBC transfusion outside the 24 hour target or two units RBCs given without a haemoglobin check between transfusions. Severe non-adherence was defined as “a transfusion was not performed in a patient whose haemoglobin level fell below the assigned threshold or a transfusion was performed in a patient whose haemoglobin level was above the assigned threshold”.

2,007 patients were recruited with data for analysis available on 2,003. The groups were well balanced. The commonest operations were coronary-artery bypass grafting only (40%), valve surgery only (30%) and combined coronary-artery bypass grafting and valve surgery (20%). 25.7% of patients had received a RBC transfusion prior to randomisation.

53.4% of patients in the restrictive-threshold group and 92.2% of patients in the liberal-threshold group received a RBC transfusion after randomisation (RR, 0.58; 95% CI, 0.54 to 0.62, P < 0.001). After randomisation, patients in the liberal-threshold group had one unit of RBCs administered. One day after randomisation, the mean nadir in the

haemoglobin level was approximately 1 g/dL lower in the restrictive-threshold group. The rates of non-adherence were 30.0% and 45.2% in the restrictive and liberal-threshold groups, respectively. The rate of severe non-adherence was 9.7% in the restrictive-threshold group and 6.2% in the liberal-threshold group.

Primary outcome data was not available for 4.8% of patients. There was no difference in the primary outcome measure; 35.1% in the restrictive-threshold group compared to 33.0% in the liberal threshold group (OR, 1.11; 95% CI, 0.91 to 1.34; P = 0.30). There was no difference in pre-specified subgroup analyses looking at higher risk patients. Mortality was higher in the restrictive-threshold group (4.2% vs. 2.6%; hazard ratio, 1.64; 95% CI, 1.00 to 2.67; P = 0.045). This higher risk of mortality persisted after sensitivity analysis, although it was a fragile result. There was no difference in serious post operative complications, excluding primary event outcomes, (35.7% in the restrictive-threshold group compared to 34.2% in the liberal-threshold group). There was no difference in any of the other secondary outcomes. The mean costs associated with RBC transfusion were £287 and £427 in the restrictive and liberal-threshold groups respectively (P < 0.001). There was no difference in the overall cost of care at three months.

Critique

Previous studies in critically ill patients had shown no difference in outcomes when restrictive and liberal transfusion thresholds were compared.[1,2] Uncertainty existed whether these results should be extrapolated to a post operative cardiac surgical patient cohort or those with unstable cardiac disease. Observational studies have demonstrated a wide range in RBC transfusion rates after cardiac surgery.[3] This study sought to answer the question whether a restrictive or liberal transfusion strategy affected post operative outcomes.

There was no difference in the primary outcome measure. The study benefited from greater power than anticipated due to a higher number of primary outcome events than expected. The investigators conclude that a lack of power cannot be responsible for the negative result. However, the issue of separation between the groups should be addressed.

The two groups were randomised to transfusion thresholds 1.5 g/dL apart. This compared to a transfusion thresholds of 3 g/dL apart in the TRICC trial and 2 g/dL apart in the TRISS trial.[1,2] This yielded only a small separation between the two groups. On day one after randomisation, the mean nadir in the haemoglobin level was approximately 1 g/dL lower in the restrictive-threshold group. The mean nadir in the haemoglobin in the restrictive group never fell below 8 g/dL, similarly, the standard deviation bars never crossed 7 g/dL during days 1-10.

The investigators designed the study with a two sided P value. Therefore, the study can be distilled into two questions; is a liberal-transfusion threshold harmful or is anaemia harmful? The trial answers the former question (92.2% of patients in the liberal-transfusion group received RBC transfusion). However, with little evidence of severe anaemia in the restrictive-threshold group and a transfusion threshold that is 0.5 g/dL higher than that in the TRICC and TRISS restrictive strategies, this study struggles to answer the question is anaemia harmful? The investigators acknowledge in their discussion that wider transfusion thresholds may have altered the results.

There was substantial non-adherence in both groups. This is a potential confounding variable. It may have been that patients in the restrictive-transfusion group were sicker and clinicians deemed it necessary to transfuse outside the protocol. In contrast, patients in the liberal-transfusion group may not have been transfused as they were well.[4] However, the authors dispute this argument stating there were equal numbers of "sick" patients in both groups at randomisation.[5] In support of this, only a a small number clinicians withdrew consent (25 in the restrictive-transfusion group and 19 in the liberal-transfusion group).

Caution should be shown in interpreting the statistically significant increase in mortality seen in the restrictive-threshold group. This was a secondary outcome for which the paper was not powered to detect. The greatest separation in the Kaplan-Meier survival curves occur between days 40 and 60, and a biologically plausible explanation is not provided for this. In addition, the number of events were small in each group (42 deaths in 1000 patients in the restrictive group compared to 26 deaths in 1003 patients in the liberal group). As a consequence, the results are "fragile" meaning a small change in number of deaths in the restrictive-threshold group would render the results non-significant.[6] With this in mind, it is worth remembering 40% of published results are reversed with time.[7]

The results of this trial are in keeping with the body of medical evidence regarding transfusion in critical ill patients. However, given that post operative cardiac patients represent a specific patient cohort, the limitations of the trial discussed above, and the use of composite outcome measures, more work needs to be done in this area to establish the true impact on mortality associated with restrictive and liberal transfusion practices.

Where it sits in the body of evidence

- The FOCUS study evaluated transfusion thresholds in 2,016 post hip-fracture surgery patients aged over 50 and at high cardiovascular risk.[14] Patients were randomly assigned to a liberal transfusion strategy (a haemoglobin threshold of 10 g/dL) or a restrictive transfusion strategy (symptoms of anaemia or at physician discretion for a haemoglobin level of <8 g/dL). A median of two units of RBCs was transfused per

patient in the liberal transfusion strategy, as compared with a median of no units in the restrictive strategy. There was no difference in the primary outcome of death or walking unaided at day-60; 35.2% in the liberal-strategy group vs. 34.7% in the restrictive-strategy group (OR, 1.01; 95% CI, 0.84 to 1.22; absolute risk difference of 0.5%; 95% CI, −3.7 to 4.7). There was no difference in the rate of in-hospital acute coronary syndrome; 4.3% and 5.2%, respectively (absolute risk difference, −0.9%; 99% CI, −3.3 to 1.6).

- The landmark TRICC study enrolled 838 critically ill patients and compared a restrictive transfusion strategy (a transfusion trigger of 7 g/dL, with a target maintenance haemoglobin of 7 - 9 g/dL) with a liberal transfusion strategy (a transfusion trigger of 10 g/dL, with a target maintenance haemoglobin of 10 - 12 g/dL).[1] 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 critical ill patients with septic shock.[5] Transfusion thresholds were similar to the TRICC study.[1] There was no difference in the primary endpoint of 90-day mortality; 43.0% of patients assigned to the lower transfusion threshold group died, as compared with 45.0% of patients assigned to the higher transfusion threshold group (RR, 0.94; 95% CI, 0.78 to 1.09; P = 0.44).

- An observational study using data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database demonstrated the variation in transfusion practices after coronary-artery bypass grafting.[2] Data involving 82,466 cases from 408 sites who conducted at least 100 on-pump CABG operations per year were analysed. The rates of RBC transfusion ranged from 7.8% to 92.8%. Case mix, geographic location, academic status, and hospital volume (P < 0.001) only partly accounted for this wide variation.

- The Cochrane Collaborative conducted a meta-analysis of trials comparing restrictive with liberal transfusion practices. Many of these trials included patients with stable cardiac disease but not acute coronary syndrome. Patients allocated to restrictive transfusion had a lower in hospital (RR, 0.77; 95% CI, 0.62 to 0.95) but not 30-day mortality (RR, 0.85; 95% CI, 0.70 to 1.03).[8]

- In a study of patients with acute upper gastrointestinal bleeding, a restrictive transfusion threshold was associated with a reduction in mortality.[9] Mortality at 6 weeks was 5% in the restrictive-strategy group compared to 9% in the liberal strategy group (hazard ratio, 0.55; 95% CI, 0.33 tp 0.92; P = 0.02). Further bleeding was less common in the restrictive-strategy group (P = 0.01). A rise in portal pressure following transfusion was suggested as the mechanism for this harmful response.

- The ABLE trial randomised patients to receive RBC less than 8 days old compared with the oldest compatible unit available in the blood bank.[10] 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 – 5.5).

- The RECESS study examined the effect of transfusing RBC stored for 10 days or less (shorter-term storage group) or for 21 days or more (longer-term storage group) in patients 12 years or older undergoing complex cardiac surgery.[11] 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 to 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 1,250 g to receive either RBC less than 7 days old or standard issue RBCs.[12] 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.

- 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.[13]

Should we implement this into our practice?
This remains unclear. This trial is supported by a large body of evidence in the general ICU population. Further work should be done in a cardiac surgical population.

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The TRIGGER Trial

Jairath V, Kahan BC, Gray A, Doré CJ, Mora A, James MW, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. The Lancet. 2015 July;386(9989):137–44.

Study synopsis

This pragmatic, open-label, cluster randomised trial, examined whether a restrictive versus liberal transfusion policy in acute upper gastrointestinal haemorrhage was feasible and safe to implement. As patients with upper gastrointestinal bleeding may present via a number of routes, be managed by different specialities and require immediate treatment, a randomised controlled trial may prove difficult. A feasibility trial was undertaken to ascertain if clinician behaviour could be altered. A cluster design was chosen to simplify the process and to reduce contamination between groups. This study aimed to inform the design of a phase 3 trial, however, outcome measures were also recorded.

To be eligible for inclusion, hospitals had to have more than 400 beds, have more than 20 upper gastrointestinal bleeds per month, have a 24 hour endoscopy service and on site intensive care facilities. Patients aged 18 and older were eligible if they had new acute upper gastrointestinal bleeding (i.e. haematemesis or melaena), irrespective of co-morbidities. Patients with exsanguinating haemorrhage were excluded.

Patients managed using the restrictive policy had a transfusion trigger of 80 g/L, with a target haemoglobin of 81 – 100 g/L. In the liberal policy, patients were transfused if their haemoglobin fell below 100 g/L, with a target haemoglobin concentration of 101 – 120 g/L. Clinicians were not blinded to the intervention.

The following outcomes were measured to assess feasibility; recruitment rate, adherence to transfusion policy, difference in haemoglobin concentration, red blood cell (RBC) exposure, and evidence of selection bias. Additional outcome measures included RBC use, incidence of further bleeding, thromboembolic and ischaemic events, infection rate, adverse events, health-related quality of life, need for therapeutic intervention (endoscopy, surgical or radiological), transfusion reactions and mortality.

The six participating hospitals were randomly assigned in permuted blocks of six (three hospitals per policy), without stratification or matching to either restrictive or liberal transfusion policy. 849 patients were required to provide a 92% power to detect a 1 point difference in Rockall score using a two-sided significance level of 5%.

Over a six month period, 936 patients were recruited. There were some imbalances in the comorbidities between groups, however Rockall and Blatchford risk scores were similar, as were blood pressure, heart rate, and symptoms of bleeding. 3% of patients were ineligible due to exsanguination. The recruitment rate was higher in the liberal policy (62% of eligible patients vs 55%; P = 0·04).

There was no difference in the number of patients transfused; 46% of patients in the liberal policy group compared to 33% of patients in the restrictive policy (P = 0.23). Protocol adherence was assessed by a number of haemoglobin deviations outside the target range. Adherence was better in the restrictive policy than the liberal policy, 96% compared to 83% (P = 0.005). There was no difference in the mean number of RBC units transfused; restrictive policy 1.2 versus liberal policy 1·9 (difference, –0·7; 95% CI, –1·6 to 0·3, P = 0·12). Similarly, there was no difference in mean haemoglobin during the follow up period.

There was no significant difference in the clinical outcomes including further bleeding, 28-day mortality, length of stay, rate of thromboembolic or ischaemic events, serious adverse events or health-related quality of life.

Critique

In 2013 Villanueva and colleagues published a single centre trial involving 921 patients looking at transfusion strategies in acute upper gastrointestinal haemorrhage.[1] The TRIGGER trial is the first multi-centre randomised controlled trial looking at transfusion thresholds in this patient population. Although this was primarily designed as a feasibility study, the fact that it is the first multi-centre trial and also the largest trial in this area make it noteworthy.

The pragmatic nature of this trial with a wide inclusion criteria resulted in a rapid recruitment rate. 96% of patients presenting to hospital with an acute upper gastrointestinal bleed were eligible and almost 60% were recruited. The cluster design of this trial seems to have added to the ease of implementation of the transfusion strategy and speed of recruitment. Unlike the paper by Villanueva and colleagues, this trial also included patients with ischaemic heart disease, vascular disease or stroke.[1] These conditions are present in approximately 40% of patients with acute upper gastrointestinal bleeds in the UK.[2] If replicated in a phase three trial, it would produce results that are applicable to almost all patients with an upper gastrointestinal bleed.

The authors comment on a trend towards increased mortality in patients with ischaemic heart disease managed with a restrictive transfusion policy. A previous pilot study involving 110 patients with acute coronary syndromes or stable angina undergoing cardiac catheterisation examined the impact of a restrictive transfusion policy (transfusion threshold 80 g/L) versus liberal transfusion policy (transfusion threshold

100 g/L).[3] There was a higher mortality in the restrictive transfusion group, however the patients in this group were older, more likely to be suffering from a non-STEMI and had greater comorbidities. These results contradict the findings in a general ICU population, a postoperative cardiac surgical population, and an elderly post hip fracture surgery population.[4,5,9] This highlights the need for more high quality studies examining the impact of a restrictive transfusion strategy in those with ischaemic heart disease.

This trial was primarily conducted to inform the design of a future phase three study. The results from this trial raises the question whether is there still equipoise for restrictive and liberal transfusion thresholds. The overall adherence to the transfusion protocol was higher in the restrictive policy arm. Indeed, the adherence in patients managed with the liberal policy decreased during the six month study period, whereas it remained consistent in patients managed with the restrictive policy. 672 of the 675 protocol violations in the liberal transfusion arm were for clinicians not transfusing despite a haemoglobin concentration of less than 100 g/L. This indicates clinicians are moving away from liberal transfusion, even in the setting of acute haemorrhage. The publication of the trial by Villanueva and colleagues, four months into the study period, which demonstrated a reduction in mortality and rebleeding rate with a restrictive transfusion threshold of 70 g/dL, may have impacted on this.[1] To address these concerns the investigators propose further work uses revised transfusion thresholds of 70 g/L in the restrictive arm and 90 g/L in the liberal arm. This may go some way to achieving equipoise.

There were a number of imbalances between the two groups at baseline. Patients managed with restrictive policy were more likely to have respiratory disease and hypertension but were on average 2.4 years younger. Patients managed with the liberal policy were more likely to have liver disease and bleeding due to a gastro-oesophageal varix. This may represent inherent bias in the recruitment process as clinicians were unblinded as to the treatment allocation. However, the major reason for not recruiting into the trial was patient choice, rather than physician choice. The imbalances may be less likely in an individual patient trial.

Cluster randomised trials are becoming increasingly common.[7] Increasing variance within each group results in a greater number of participants needed to achieve adequate power. With such a broad inclusion criteria this is a problem the investigators may face when conducting future work. However, the impressive speed of recruitment in this feasibility study, partly attributable to its inclusive criteria, demonstrate the authors can overcome this obstacle, and in doing so, produce a phase three trial applicable to the majority of patients with acute upper gastrointestinal bleeding.

Where it sits in the body of evidence

- Villanueva and colleagues conducted a single centre randomised trial comparing a transfusion threshold of 70 g/L (restrictive group) with 90 g/L (liberal group) in 921 patients with acute upper gastrointestinal bleeding.[1] Low risk patients with a Rockall score of 0 or a haemoglobin of greater than 120 g/L were excluded. Patients with acute coronary syndrome, symptomatic peripheral vascular disease, and cerebral vascular disease were also excluded. 51% of the liberal transfusion group received RBC transfusion compared with 14% of the restrictive transfusion group (P < 0.001). Survival was higher in the restrictive group (95% vs. 91%; hazard ratio for death, 0.55; 95% CI, 0.33 - 0.92; P = 0.02). Rebleeds were also less common in the restrictive group (10% compared to 16%; P = 0.01). Harm from liberal transfusion was ascribed to increased portal pressures.

- A pilot study involving 110 patients with acute coronary syndromes or stable angina undergoing cardiac catheterisation examined the impact of a restrictive transfusion policy (transfusion threshold 80 g/L) versus liberal transfusion policy (transfusion threshold 100 g/L).[3] The primary endpoint was a composite of death, myocardial infarction, or unscheduled revascularisation within 30 days of randomisation. The primary endpoint was seen in 10.9% (n = 6) of the liberal group and 25.5% (n = 14) of the restrictive group (risk difference,15.0%; 95% CI, 0.7% - 29.3%, P = 0.054). Thirty day mortality was higher in the restrictive group (7 deaths compared to 1 in the liberal group, P = 0.032). However, the restrictive group were on average 7 years older, more likely to be suffering from a non-STEMI and had a greater burden of co-morbidities. The number of events in this study was small.

- The landmark TRICC study enrolled 838 critically ill patients and compared a restrictive transfusion strategy (a transfusion trigger of 7 g/dL, with a target maintenance haemoglobin of 7 - 9 g/dL) with a liberal transfusion strategy (a transfusion trigger of 10 g/dL, with a target maintenance haemoglobin of 10 - 12 g/dL).[4] There was no difference in 30 day mortality between the two groups (18.7% in the restrictive group compared with 23.3% in the liberal group, P = 0.11).

- The TRISS study examined the role of restrictive and liberal transfusion thresholds in critical ill patients with septic shock.[5] Transfusion thresholds were similar to the TRICC study.[4] 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 (RR, 0.94; 95% CI, 0.78 to 1.09; P = 0.44).

- The TITRe2 trial examined the impact of using a restrictive transfusion threshold (threshold for transfusion 7.5 g/dL) compared to a liberal transfusion threshold (threshold for transfusion 9 g/dL) in patients following cardiac surgery.[6] 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 2,007 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).

- A meta-analysis was carried out of trials comparing restrictive with liberal transfusion strategies.[8] Thirty-one randomised controlled trials involving 9,813 patients were included. Patients allocated to a restrictive transfusion group were less likely to receive RBC transfusions (RR, 0.54; 95% CI, 0.47 - 0.63) and had a lower average number of RBC transfused (mean difference −1.43; 95% CI, −2.01 to −0.86). There was no statistically significant difference in mortality, morbidity, fatal or non-fatal myocardial infarctions.

- The FOCUS study evaluated transfusion thresholds in 2,016 post hip-fracture surgery patients aged over 50 and at high cardiovascular risk.[10] Patients were randomly assigned to a liberal transfusion strategy (a haemoglobin threshold of 10 g/dL) or a restrictive transfusion strategy (symptoms of anaemia or at physician discretion for a haemoglobin level of <8 g/dL). A median of two units of RBCs was transfused per patient in the liberal transfusion strategy, as compared with a median of no units in the restrictive strategy. There was no difference in the primary outcome of death or walking unaided at day-60; 35.2% in the liberal-strategy group vs. 34.7% in the restrictive-strategy group (OR, 1.01; 95% CI, 0.84 to 1.22; absolute risk difference of 0.5%; 95% CI, −3.7 to 4.7). There was no difference in the rate of in-hospital acute coronary syndrome; 4.3% and 5.2%, respectively (absolute risk difference, −0.9%; 99% CI, −3.3 to 1.6).

Should we implement this into our practice?
No. As a feasibility study this trial should not influence our current practice, but forms the foundation for a phase III study.

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The RECOVER Trial

Walsh TS, Salisbury LG, Merriweather JL, Boyd JA, Griffith DM, Huby G et al. Increased Hospital-Based Physical Rehabilitation and Information Provision After Intensive Care Unit Discharge. The RECOVER Randomized Clinical Trial JAMA Internal Medicine 2015 Apr 13; 175; 6: 901-10.

Study synopsis

This was a randomised, parallel group trial performed in two Scottish hospitals. The primary aim was to investigate the effect of increasing physical and nutritional rehabilitation after intensive care discharge on subsequent physical disability at three months.

Adult patients admitted to the ICU, who were ventilated for more than 48 hours, were eligible for recruitment when ready for discharge to a ward environment. Patients were excluded if they had a primary neurological diagnosis, were for palliative care treatment, had ongoing ventilation requirements or were discharged to a nonstudy hospital.

Recruited patients were randomized using a telephone based service. Randomisation was stratified using age (> 65 vs ≤ 65 years), disability at study entry (Rivermead Mobility Index[1] [RMI] of 0 - 5 vs 6 - 10 vs 11 - 15), nutritional status (using the physical component of the Subjective Global Assessment tool[2]), the presence or absence of delirium (using the Confusion Assessment Method for the ICU tool,[3] and the ward destination (surgical vs medical). After ICU discharge, both groups received physiotherapy and dietetic, occupational, and speech and language therapy. The standard group received usual ward care, with the addition of a self help ICU rehabilitation manual previously associated with improved physical recovery.[4] The intervention group had a dedicated trained rehabilitation practitioner who co-ordinated and delivered an individualized rehabilitation program including goal setting, with the aim to deliver higher levels of mobilization, exercise, relevant dietetic therapy, occupational therapy, and speech and language therapy compared with usual care.

The primary outcome was the RMI at 3 months after randomisation. Secondary end points included post-ICU length of stay, readmission to the ICU, hospital survival, and RMI before hospital discharge. Patient reported outcome measures at 3, 6, and 12 months after randomization included the Physical and the Mental Component Summary scores of the 12-Item Short Form Health Survey,[5] the Hospital Anxiety and Depression Scale[6], the Davidson Trauma Scale[7] and self-reported symptom scores using visual analogue scales for fatigue, breathlessness, appetite, pain, and joint stiffness. At three months grip strength and mobility were also tested.[8]

The sample size calculation was based on a predefined improvement in the RMI of 2 at

three months. To detect this difference 100 patients were required per group (80% power; 5% significance). The authors assumed a 12% death rate with 5% loss to follow up, necessitating 240 patients.

A total of 828 patients were screened and subsequently 240 patients were randomised. Baseline characteristics were well matched. At three months, 6 patients in each group had died. Intervention patients received 2 to 3 times more frequent physiotherapy, more dietetic reviews (95% vs 67%), had higher nutritional intake and also more occupational therapy interventions (43% vs33%).

For the primary outcome, the median RMI at randomisation was 3 (IQR, 1 - 6) and at 3 months, 13 (IQR, 10 - 14) for the intervention and usual care groups (mean difference, –0.2 [95% CI, –1.3 to 0.9; P = 0.71]) indicating no significant treatment effect. The HRQOL scores were unchanged by the intervention. No differences were found for self-reported symptoms of fatigue, pain, appetite, joint stiffness, or breathlessness. Levels of anxiety, depression, and post-traumatic stress were similar, as were hand grip strength and the timed Up & Go test. No differences were found at the 6- or 12- month follow-up for any outcome measures.

Critique

Patients who survive critical illness often suffer both physical and psychological impairment long after discharge from the intensive care and hospital setting[9]. Muscle atrophy is common and occurs early in critical illness.[10] However, whether weakness leading to functional impairment is an inevitable part of critical illness, or is modifiable, has not been fully addressed. Evidence suggests early interventions in the ICU may make a difference.[11,12] However, early rehabilitation may not always be practical or even possible. Post intensive care rehabilitation trials, however, have not been able to demonstrate improved outcomes.[13-15] This trial examined an intervention designed to meet individual patients' needs using multidisciplinary support overseen by a multi skilled rehabilitation assistant. Such an approach contrasts previous unsuccessful trials..

This was an interesting study using multiple interventions in an attempt to improve patient function. There are many positive aspects to this trial. The investigators performed a pilot study to assess the feasibility of the intervention, and showed its delivery was possible while gaining vital experience in the process.[16] The results of the pilot were also used in the sample size calculation. There was an appropriate telephone randomization process, with stratification based on seemingly relevant issues relating to rehabilitation potential. The process produced groups with similar baseline characteristics, and hence, potentially similar rehabilitation potential. These were sick patients, representative of the general ICU population - three quarters required inotropes and the median duration of ventilation was 8 - 9 days.

The intervention group received more frequent physiotherapy (which approximated to twice as many transfers and walks, and more exercise), and dietetic and occupational therapy support. Furthermore, the outcome assessors were blinded. In the follow up period, the trial incorporated an impressive range of potential measures of both physical and psychological recovery, collating large amounts of data on post critical illness patients. Finally, an economic evaluation was performed.

Despite the detailed design of this trial, there are still limitations, some of which highlight the problems of conducting rehabilitation research in critical illness. The trial only randomised 50% of eligible patients, for two main reasons; randomisation problems and patients declining to participate. The failure to randomise patients could have affected the outcome, as patients who consent to a rehabilitation trial may form a self selected group of motivated individuals. Thus less motivated individuals, who may benefit from more intensive rehabilitation, were not included. The intervention in this trial was individually planned for each patient and the intervention group received more interactions. However, although the relative rate of rehabilitation events were greater than the usual care group, the absolute difference in the numbers of these events was small and it is unclear how long each intervention lasted or what the intensity of the activity was. The length of the program also varied. The post ICU stay was approximately eleven days, so perhaps a longer intervention would be more beneficial. These patients were still significantly physically impaired on discharge. Essentially, the exact recipe for the timing, frequency, intensity and length of any program is unknown.

A further issue with the performance of rehabilitation trials is the outcome measurement, with this trial using a variety of physical and psychological tests. The main outcome measure was the RMI, which is a functional mobility scale used in stroke research. Its discriminatory ability in ICU survivors is unclear. While many patients achieved good RMI scores, major morbidities remained, as highlighted by persistent impairment in health status, psychological distress, and symptoms in the trial. The rehabilitation manual was received by both groups and could lessen the difference in rehabilitation achieved by the two groups.. Furthermore, it is unclear what rehabilitation was available after discharge, and we can only presume there was similar access to further therapy.

The investigators concluded increased frequency and intensity of mobility, exercise, dietetic, and related therapies for patients discharged from the ICU, during the post-ICU hospital stay, and greater provision of information, did not improve measures of physical function or HRQOL compared with the usual practice. The RECOVER study adds much useful information to this field, and generates many further questions, in terms of patient selection, timing of rehabilitation (perhaps earlier is better) and the constituents of the program.

Where it sits in the body of evidence

- In an early three centre trial, 126 ventilated patients treated in the ICU for more than 48 hours were randomised to either a control consisting of ward visits, telephone follow up, and appointments at 8 weeks and 6 months or to the intervention consisting of the same plus a 6 week self-help rehabilitation manual.[4] The intervention group improved, compared with the control patients, on the Short-Form Health Survey physical function scores at 8 weeks and 6 months (P = 0.006), and there was a trend to a lower rate of depression at 8 weeks (12% vs. 25%). There were no differences in levels of anxiety and PTSD-related symptoms between the groups.

- In a multi-centre, randomised trial in the United Kingdom, using a nurse led intensive care follow-up programme, 286 patients were randomised to a manual-based, self-directed, physical rehabilitation programme or usual care.[15] The main outcome measure was health related quality of life (measured with the SF-36 questionnaire) at 12 months after randomisation. One hundred and ninety-two patients completed the one year follow-up. At 12 months, there was no difference in the SF-36 physical component score (mean 42.0 (SD 10.6) v 40.8 (11.9) or the SF-36 mental component score (effect size, 0.4; 95% CI, -3.0 to 3.7; P = 0.83).

- In a multi-centre trial in Australia, 195 patients ventilated for more than 48 hours were randomised to a graded, individualised endurance and strength training intervention over eight weeks or control.[13] One hundred and sixty-one patients completed the 26 week assessment. Although there were significant improvements in both intervention and control at eight weeks, which persisted to 26 weeks, there was no significant difference in SF-36 physical function scale (P = 0.84), six-minute walk test or health-related quality of life (SF-36).

- In a single-centre, assessor-blinded trial, 150 participants were stratified and randomized to receive usual care or intervention if they were in the ICU for 5 days or more.[14] The intervention group received intensive exercises in the ICU, ward and outpatients for 8 weeks. Physical function was evaluated using the Six-Minute Walk Test (primary outcome), the Timed Up and Go Test and the Physical Function in ICU Test. Patient-reported outcomes were measured using the Short Form 36 Health Survey, version 2 and Assessment of Quality of Life Instrument. No significant differences were found for the primary outcome of Six-Minute Walk Test or any other outcomes at 12 months after ICU discharge.

- In a smaller controlled trial, with later recruitment up to 16 weeks, 59 patients were randomised to two weekly sessions of physiotherapist-led cycle ergometer exercise, plus one equivalent unsupervised exercise session, versus usual care for an eight week period.[17] There was a large dropout rate of > 50%. The intervention resulted in a small improvement in anaerobic threshold of 1.8 (95% CI, 0.4 – 3.2) ml O2/kg/min, which was

not sustained at six months.

Should we implement this into our practice?
Not on the available evidence. Post intensive care rehabilitation currently does not seem to have a significant or lasting effect. At present, there remains a lack of quality evidence in this area.[18]

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The ProMISe Trial

Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al for the ProMISe Trial Investigators. Trial of Early, Goal-Directed Resuscitation for Septic Shock. New England Journal of Medicine. 2015 Apr 2;372(14):1301–11.

Study synopsis

This was a pragmatic, open label, multi-centre, randomised, controlled trial comparing early goal directed therapy (EGDT) with usual-care in septic shock. The study was conducted in 56 NHS hospitals in England. The primary outcome was 90-day mortality. The investigators also included a cost effectiveness analysis to examine the resource utilisation associated with both groups.

Patients aged 18 and over with septic shock were eligible for enrolment if they were within 6 hours of presentation to the emergency department. The first dose of antibiotics had to be administered prior to randomisation. The following definitions were used for recruitment:

- presumed infection plus two or more SIRS criteria, and
- refractory hypotension (systolic blood pressure (SBP), < 90 mmHg; or mean arterial pressure (MAP), < 65 mmHg, despite resuscitation with at least 1L of intravenous fluids) or blood lactate level ≥4 mmol/L.

The usual care group were monitored and treated at the discretion of the treating clinicians. The EGDT group received 6 hours of protocolised care, which consisted of the following interventions:

- Supplemental oxygen to achieve a SpO2 ≥ 93%
- A central venous catheter capable of continuous $ScvO_2$ monitoring
- A 500 ml crystalloid or colloid fluid bolus every 30 minutes until CVP ≥ 8mmHg
- If CVP ≥ 8mmHg and MAP < 65mmHg or SBP < 90mmHg a vasopressor was added
- Once MAP > 65mmHg or SBP > 90mmHg, $ScvO_2$ was considered:
  - if $ScvO_2$ was < 70%, red blood cells (RBC) were transfused until a haemoglobin of > 10 g/dL
  - If haemoglobin > 10 g/dL, dobutamine was added (maximum dose 20 µg/kg/min)

ICNARC data estimated 40% 90-day mortality in the usual care group. Enrolling 1,260 patients would have an 80% power to detect a 20% relative risk reduction in mortality. These power calculations took into account lower than expected mortality in the ProCESS and ARISE trials.[1,2]

Over 3 years, 6,192 patients were screened and 1,260 patients were enrolled, 98.7% of whom were included in the final analysis. The groups were evenly matched, including the

number of patients with refractory hypotension, hyperlactaemia or both. Both groups had approximately 2L of fluid prior to randomisation.

A $ScvO_2$ monitor was not inserted in 80 patients in the EGDT group. A standard CVC was inserted in 50.9% of the usual-care group. Patients in the EGDT group received more IV fluids in the first 6 hours of resuscitation (2,000 ml in EGDT group vs 1,784ml in the usual care group). In the first 6 hours, patients in the EGDT group received more vasopressors, more dobutamine (18.1% vs 3.8%) and were more likely to receive RBC transfusions (8.8% vs 3.8%). At the end of 72 hours, including the period prior to randomisation, the amount of fluid administered was 7,573 ml in the EGDT group vs 7,765 ml in the usual care group. There was no difference in CVP, MAP, SBP or haemoglobin at the end of the 6 hour intervention period.

The 90-day mortality was similar in both groups; 29.5% in the EGDT group vs 29.2% in the usual care group (relative risk, 1.01; 95% CI, 0.85 - 1.20, P = 0.90). Patients in the EGDT group were more likely to have received advanced cardiovascular support (37.0% vs 30.9%, P = 0.026) and had longer ICU lengths of stay (2.6 days vs 2.2 days, P = 0.005). There were no other differences in secondary outcomes. There was no difference in the average cost of care £12,414 in the EGDT group vs £11,424 in the usual care group (P = 0.26).

Critique

This was a well conducted, randomised controlled trial with good internal and external validity. As such, there are few points to critique. Importantly, ProMISe, along with ProCESS and ARISE, was one of three harmonised papers looking at EGDT. Therefore, it must be discussed in the context of the original work by Rivers and colleagues along with the ProCESS and ARISE trials.[1-3]

The work by Rivers and colleagues was seen as a turning point in management of sepsis.[3] There were concerns that, as a single centre study with results that have never been replicated, it lacked external validity. It was on this basis the three EGDT trials were conducted. Rivers work did serve to heighten the awareness of sepsis and became the cornerstone of surviving sepsis guidelines.[4] That the mortality seen in these three trials was 18 - 29% in both groups, compared with 46.5% in usual-care group in the paper by Rivers and colleagues, is probably indicative of the improved care that patients with sepsis now receive.[1-3]

The logical question then becomes has our usual care evolved to closely emulate EGDT, and therefore, was there enough separation between the two groups? In the ProMISe trial, patients in both groups received an almost identical amount of fluid (approximately 7.5L in the first 72 hours). Although there was a statistically significant difference in the amount of IV fluids administered in the first 6 hours, it may not have been clinically

significant (2,000 ml in EGDT vs 1,784ml in the usual-care group, with about 2L administered prior to randomisation). In contrast the patients in the Rivers trial had a greater difference in the amount of fluid administered at 6 hours (4,981 ml in the EGDT vs 3,499 ml in the usual-care group).[3] The heightened appreciation of resuscitation end points and clinician awareness of the treatment assignment may mean those in the usual-care group had aggressive resuscitation similar to those in the EGDT group, potentially diluting the treatment effect.

Factors which may have diluted the treatment effect of EGDT must also be considered. There was an appreciable rate of non-compliance in the EGDT group. Eighty patients (12.7%) did not have a $Scv0_2$ monitor inserted. The supplementary material would indicate that in the first 6 hours, only two thirds of patients had RBC transfused in response to low $Scv0_2$ and approximately 50 - 60% of patients had dobutamine in response to low $Scv0_2$. There was a marked difference in use of RBCs between the Rivers paper (64.1%) and the ProMISe trial (8.8%).[3] This may have diluted the treatment effect of EGDT, or conversely, it may have diluted the harmful effects of these interventions. However, the adherence-adjusted analysis compared those adherent to the EGDT protocol fully with those in the standard care group. There was no difference in mortality (relative risk, 1.02; 95% CI, 0.78 to 1.32, P = 0.90). The level of adherence was equivalent to that in ProCESS and ARISE trials.

In their discussion, the investigators remark the patients in the Rivers paper were sicker than those in the ProMISe trial (mean APACHE II score 20.4 vs 18.0, mean lactate 6.9 vs 5.1). However, patients in the ProMISe trial had lower MAP (64.7 mmHg in the ProMISe trial vs 76 mmHg in the Rivers trial).[3] It is tempting to think that EGDT may benefit sicker patients more, but subgroup analysis refutes this. In the ProMISe trial, patients with a higher SOFA score had a trend towards reduced mortality in favour of the usual care group.

The lower than predicted mortality means that small differences in outcomes may be missed. Only one third of eligible patients were recruited, with patients attending at weekends, for example, being less likely to be recruited. It may be these patients have a higher mortality, thus accounting for some of the lower that expected mortality.

From the current evidence, EGDT should now be considered equivalent to usual-care. There would appear to be wisdom in avoiding the potentially harmful aspects of EGDT, such as RBC transfusions, where possible. Credit should be given to the work done by Rivers in improving our usual-care to the point where mortality from septic shock is now 29%.

Where it sits in the body of evidence

- Rivers and colleagues conducted a single centre, randomised controlled trial

comparing EGDT with standard care in 263 patients with severe sepsis and septic shock.[3] Patients in the EGDT group had a significantly lower in-hospital mortality (30.5%) than those in the standard care group (46.5%) (P = 0.009).

- ProCESS was a randomised controlled trial conducted in 31 centres in the USA involving 1,341 patients with septic shock.[1] It compared three treatment strategies; EGDT, protocol-based standard therapy (which had resuscitation targets but did not mandate the use of a CVC and had lower thresholds for RBC transfusion), and usual care. The primary endpoint of 60-day mortality occurred in 21.0% of the EGDT group, 18.2% of the protocol-based standard therapy and 18.9% of the usual care group. There was no statistical difference in mortality between groups.

- The ANZICS Clinical Trials Group conducted the ARISE trial, comparing EGDT with usual care in 51 ICUs in Australasia.[2] This patient cohort had a lower APACHE II score (15.4 in the EGDT group) than the Rivers, ProMISe and ProCESS trials. There was no difference in 90-day mortality between the two groups (18.6% in the EGDT group vs 18.8% in the usual-care group).

- Angus and colleagues completed a meta-analysis of five trials which examined EGDT in sepsis.[5] These were ProMISe, ProCESS, ARISE, the original paper by Rivers and colleagues and a paper on lactate clearance by Jones and colleagues.[6] There were 4,735 patients in the meta-analysis, with no difference in mortality between the EGDT group (23.2 %) and control group (22.4 %) (OR, 1.01; 95% CI, 0.88 to 1.16, P = 0.9). Further analysis of the ProMISe, ProCESS and ARISE trials (n = 4,063) also demonstrated no difference in 90-day mortality (pooled OR, 0.99; 95% CI 0.86 to 1.15, P = 0.93).

- In a study of 300 patients with early sepsis and a SBP < 90 mmHg or a lactate > 4 mmol/L; EGDT targeting >10% lactate clearance as an end-point was found to be non-inferior to EGDT using $Scv0_2$ >70% as an endpoint.[6]

- The FEAST study examined the role of fluid boluses in 3,141 paediatric patients with severe febrile illness in Africa.[7] Patients were randomised to one of three groups; albumin-bolus group (20 to 40 ml per kg of 5% albumin solution), saline-bolus group (20 to 40 ml per kg 0.9% saline), or control group (no bolus). Patients with hypotension could not be randomised to the no bolus group. The trial was terminated early due to a reduced mortality seen in patients randomised to the no bolus group. The 4-week mortality was 12.2% in the albumin-bolus group, 12.0% in the saline-bolus group, and 8.7% in the control group (P = 0.004 for the comparison of bolus with control). There was a high incidence of malaria and anaemia in this study.

- The SAFE study compared the use of albumin with saline for fluid resuscitation in 7,000

critically ill patients.[8] In a subgroup analysis of 1,218 patients with severe sepsis, there was no difference in 28-day mortality (relative risk, 0.87; 95% CI, 0.74 to 1.02, P = 0.09).

- The PAC-Man trial was a pragmatic study comparing the management of 1,041 patients with and without a pulmonary artery catheter.[9] There was no difference in hospital mortality between the two groups.

- The CORTICUS study group conducted a multi-centre RCT comparing hydrocortisone with placebo in septic shock.[10] The trial was terminated early and was therefore underpowered. There was no difference in 28 day mortality. Post hoc analysis showed patients in the hydrocortisone group had earlier reversal of shock; 3.3 days (95% CI, 2.9 to 3.9) versus 5.8 days (95% CI, 5.2 to 6.9). However, patients in the hydrocortisone group had more episodes of superinfection (combined OR, 1.37; 95% CI, 1.05 to 1.79).

- The ADRENAL study (NCT01448109), currently in progress, is a large ANZICS randomised controlled trial investigating hydrocortisone in 3,800 patients with septic shock and has a primary outcome of 90-day mortality. This study will further inform the management of patients with septic shock.

- Ferrer and colleagues conducted a retrospective analysis of 17,990 patients with severe sepsis and septic shock.[11] They found a linear increase in mortality for every hour antibiotics were delayed.

Should we implement this into our practice?

Yes. The interventions and additional resources used in the original Rivers trial do not add to high quality usual care sepsis management.

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Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: A randomized clinical trial. JAMA. 2015 Feb 17;313(7):677–86.

Study synopsis

Although meta-analysis of small trials has shown steroids reduce mortality in patients with severe community-acquired pneumonia, a larger study was recommended.[1] This study hypothesised corticosteroids may modulate the inflammatory response and reduce treatment failure in patients with severe community-acquired pneumonia and a high CRP.

This was a multi-centre, randomised, double-blind, placebo-controlled trial conducted in three teaching hospitals in Spain, and was carried out over an eight year period. Patients over the age of 18 were deemed eligible if they met the following criteria: symptoms of community-acquired pneumonia (nosocomial pneumonia was excluded), new chest radiograph infiltrates, severe community-acquired pneumonia as defined by modified American Thoracic Society criteria or risk class V for the Pneumonia Severity Index, and a CRP > 150 mg/L.[2,3]

There was extensive exclusion criteria which included prior treatment with corticosteroids, nosocomial pneumonia, significant immunosupression, a life expectancy of less than 3 months, uncontrolled diabetes mellitus, major gastrointestinal bleeding within the last 3 months, and treatment with greater than 1 mg/kg/day of methylprednisolone or equivalent.

The intervention consisted of either intravenous methylprednisolone (0.5 mg/kg 12 hourly) or placebo for 5 days and was commenced within 36 hours of hospital admission. Antibiotic therapy was as per the American Thoracic Society guidelines.[4]

The primary outcome measure was treatment failure, which could be early, late or both. Early treatment failure (within 72 hours of initiating treatment) was defined as clinical deterioration including development of shock, need for invasive mechanical ventilation or death. Late treatment failure, occurring between 72 and 120 hours after initiating treatment, was defined as radiographic progression (increase of ≥ 50% of pulmonary infiltrates compared with baseline), development of shock, persistence of severe respiratory failure (PaO_2:FiO_2 ratio < 200 mmHg, with respiratory rate ≥ 30 breaths/min in non-intubated patients), need for invasive mechanical ventilation, or death.

One of the secondary outcome measures was time to clinical stability, defined as

temperature ≤ 37.2°C, heart rate ≤ 100 / min, systolic blood pressure ≥ 90 mmHg, and PaO_2 ≥ 60 mmHg on room air. The sample size calculation was based on an expected treatment failure rate of 35% in the placebo group. To detect an absolute reduction in treatment failure of 20%, 60 patients were required in each group (using a 2-sided type I error of 0.05 and 80% power).

One hundred and twenty patients were randomised, with 112 completing the study. There were some imbalances in the groups at baseline. The placebo group had a higher incidence of septic shock, 29%, compared to 19% in the methylprednisolone group. Seventy-five per cent of patients were admitted to ICU at the time of enrolment. Antibiotic treatment was deemed adequate in 97% of patients in each group. There was no difference in time to first antibiotic dose between the two groups.

There were eight treatment failures in the methylprednisolone group (13%) compared with 18 in placebo group (31%) (P = 0.02). Methylprednisolone reduced the risk of treatment failure (odds ratio, 0.34; 95% CI, 0.14 to 0.87; P = 0.02). This effect persisted after logistic regression analysis. The difference in treatment failure was primarily due to differences in rates of radiographic progression, however, the difference in late treatment failure remained on post hoc analysis when radiographic failure was excluded. There was no difference in hospital mortality or complications between the two groups. There was no difference in time to clinical stability (P = 0.13).

Critique

The major discussion point in this trial surrounds the use of composite outcomes. The reduction in treatment failure seen was as a result of differences in rates of radiographic progression; there were eight more cases in the placebo group. In the prospective analysis, there was no difference between groups in outcomes that are meaningful to patients, namely early mechanical ventilation, early septic shock, late respiratory failure, late mechanical ventilation, late septic shock or death. Similarly there was no difference in the secondary outcomes of time to clinical stability, ICU length of stay or hospital length of stay.

Late treatment failure could occur for more that one reason and the investigators point to a higher number of cases of late septic shock in the placebo group (4 cases) compared to the methylprednisolone group (0 cases). Indeed, *post hoc subgroup analyses* were used to show the differences in treatment failure remained when radiographic progression was excluded from analysis; two patients in the methylprednisolone group compared to 8 patients in the placebo group (P = 0.04).

Logistic regression analysis was used to adjust for imbalances in the groups at baseline. The incidence of septic shock at baseline was 29% in the placebo group and 18% in the methylprednisolone group. Thirty per cent of patients in the methylprednisolone group

were managed at ward level throughout the study, compared to 20% in the placebo group (no patients were admitted to the ward and later transferred to ICU in either group). This suggests the placebo group were sicker on admission and tended to remain so.

The authors only observed patients for 120 hours for the primary outcome measure. The Kaplan-Meier analysis shows that most treatment failures occurred between day 4 and 5. It is unclear whether a longer course of treatment (or observation) would alter the outcome of this trial, either in favour of methylprednisolone treatment or in favour of placebo (due to higher incidence of superinfection or adverse events).

The overall use of macrolide antibiotics was low in both groups (23% in the placebo group and 24% in the methylprednisolone group), and was highlighted as a cause for concern in the associated editorial.[5] In a retrospective analysis of 409 patients with bacterial pneumococcal pneumonia, the use of macrolide antibiotics in conjunction with a beta-lactam antibiotic is associated with a reduction in mortality.[6] Asadi and colleagues completed a meta-analysis on the use of macrolide antibiotics in patients with community acquired pneumonia. This study included a mix of randomised controlled trials and observational studies totalling 137,574 patients. Overall, macrolide use was associated with a reduced mortality (RR, 0.78; 95% CI, 0.64 to 0.95; P = 0.01). However, this effect was not seen in patients included in randomised controlled trials or those who had guideline concordant antibiotic regimens (as was the case in this study). Asadi went on to conclude that “guideline concordance is more important than choice of antibiotic when treating community-acquired pneumonia”.[7]

The trial was powered assuming a 35 % treatment failure in the placebo group. Interestingly, the trial upon which this is based used slightly different definitions for treatment failure.[8]

The slow recruitment rate of approximately 5 patients per year in each centre and relatively high exclusion rate (519 patients were screened and 399 were excluded), indicate this intervention is likely to benefit a low number of patients. In addition, issues such as the composite outcome measure, the use of non-patient centred outcomes and the short follow up period mean this trial probably does not represent strong enough evidence to implement methylprednisolone in the general management of patients with community-acquired pneumonia. Further research should be done to fully elucidate the role of steroids in pneumonia.

Where it sits in the body of evidence

- Blum and colleagues conducted a multi-centre RCT comparing prednisolone 50 mg once daily with placebo in 785 patients with community-acquired pneumonia.[9] Patients treated with prednisolone achieved clinical stability (a composite outcome of vital signs, mental status and oral intake) earlier than patients treated with placebo (3·0 days vs. 4·4 days).

- A meta-analysis examining the use of steroids in acute exacerbations of COPD suggested that, in comparison to placebo, steroids reduce the risk of treatment failure (RR, 0.54; 95% CI, 0.41 to 0.71).[10] The route of administration of steroids (oral or IV) or drug choice (methylprednisolone, hydrocortisone or prednisolone) did not alter the beneficial effect of steroids. Hyperglycaemia was significantly increased in the corticosteroid treatment group (RR, 5.88; 95% CI, 2.40 to 14.41).

- The ARDSnet group examined the role of methylprednisolone (2 mg/kg loading followed by 0.5 mg/kg 6 hourly for 14 days, 0.5 mg/kg 12 hourly for 7 days, then a tapering dose) in patients with established ARDS (7 to 28 days after onset).[11] There was no difference in 60-day or 180-day mortality.

- In a small study (n = 91) looking at the role of steroids in early ARDS (< 72 hours), patients treated with methylprednisolone were more likely to achieve a 1 point reduction in their lung injury score at 7 days (69.8% vs 35.7%; P = 0.002).[12] A number of secondary outcomes were also positive in favour of methylprednisolone, including reduced duration of ventilation, ICU length of stay and ICU mortality.

- The CORTICUS study group conducted a multi-centre RCT comparing hydrocortisone with placebo in septic shock.[13] The trial was terminated early and was therefore underpowered. There was no difference in 28-day mortality mortality. Post hoc analysis showed that patients in the hydrocortisone group had earlier reversal of shock 3.3 days (95% CI, 2.9 to 3.9) versus 5.8 days (95% CI, 5.2 to 6.9). However, patients in the hydrocortisone group had more episodes of superinfection (combined odds ratio, 1.37; 95% CI, 1.05 to 1.79).

- In a meta-analysis of 20 trials studying the effect of hydrocortisone in patients with severe sepsis or septic shock, patients treated with hydrocortisone had a lower 28 day mortality (35.3%) than controls (38.5%) (risk ratio, 0.84; 95% CI, 0.71 to 1.00, P = 0.05).[14]

- The MRC CRASH trial looked at the role of corticosteroids in traumatic brain injury and found those treated with methylprednisolone were more likely to be dead or severely disabled at 6 months.[15]

Should we implement this into our practice?
No. The small patient numbers, prolonged duration of the study and non-patient centred outcomes all suggest this trial requires to be replicated before adoption. The ESCAPe trial is a larger study currently investigating this issue.
(ClinicalTrials.gov website. ESCAPe trial: NCT01283009.)

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Kaukonen – SIRS Criteria for Sepsis

Kaukonen K-M, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis. New England Journal of Medicine. 2015 Apr 23;372(17):1629–38.

Study synopsis

This study examines the benefit of using two or more systemic inflammatory response syndrome (SIRS) criteria as a cut off for diagnosis of sepsis. The investigators hypothesised in the first 24 hours of ICU admission, the presence of two or more SIRS criteria would have a low sensitivity and validity in predicting mortality. They postulated mortality would increase linearly with each additional SIRS criterion and the presence of two criteria would not mark a transition point for increased mortality.

This was a retrospective analysis of data from the Australia and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD). This included 172 ICUs in Australia and New Zealand from 2000 to 2013 inclusive.

Patients with severe sepsis, i.e. infection and organ failure, were included. The diagnosis of infection was based on APACHE III scores on admission to ICU. Organ failure was defined as a SOFA score of 3 or higher. Only data from the first 24 hours of ICU admission was used. Patients were categorised into two groups; those with severe sepsis and two or more SIRS criteria (SIRS-positive severe sepsis) or those with severe sepsis and less than two SIRS criteria (SIRS-negative severe sepsis).

Multivariable logistic regression analysis was used to identify independent differences at baseline that existed between patients with SIRS-positive severe sepsis and SIRS-negative severe sepsis. The primary outcome measure was in-hospital mortality.

Data was available for 109,663 patients with severe sepsis; 87.9% had SIRS-positive severe sepsis and 12.1% had SIRS-negative severe sepsis. 20% of patients with SIRS-negative sepsis did not fulfil any SIRS criteria, and the remaining 80% fulfilled one SIRS criterion.

In comparison to patients with SIRS-negative severe sepsis, those with SIRS-positive severe sepsis tended to be younger (median age 65.8 years compared to 68.3 years, $P < 0.001$), had higher APACHE III scores, were more likely to have septic shock, require mechanical ventilation and have acute kidney injury.

The overall mortality was higher in patients with SIRS-positive severe sepsis (24.5%) than those with SIRS-negative severe sepsis (16.1%). When compared to APACHE III predicted mortality, patients with SIRS-negative severe sepsis had a higher than predicted

mortality (actual mortality 16.1%, predicted mortality 11%). There was less discrepancy in predicted and observed mortality in SIRS-positive severe sepsis (actual mortality 24.5%, predicted mortality 24%).

When mortality trends were assessed, a decrease in mortality was seen over time; there was 1.3% absolute decrease in mortality with each year. This was the same in both groups. Over a 14 year period, mortality fell in the SIRS-positive group from 36.1% to 18.3% ($P < 0.001$) and in the SIRS-negative group from 27.7% to 9.3% ($P < 0.001$).

A modified logistic regression analysis was conducted with the SIRS components removed to look at factors predicting the risk of death. Being SIRS-positive was independently associated with an increased risk of mortality (odds ratio, 1.26; 95% CI, 1.18 to 1.34; $P < 0.001$). In addition, a linear 13% increase in mortality was seen with the presence of each additional SIRS criterion (odds ratio for each additional criterion, 1.13; 95% CI, 1.11 to 1.15; $P < 0.001$). As hypothesised, there was no transitional increase in risk when two or more SIRS criteria were met.

Critique

This thought-provoking epidemiological study from a large cohort of ICU patients challenges the traditional application of SIRS criteria. A variety of conditions such as trauma, burns, and pancreatitis induce an inflammatory response. Therefore, the SIRS criteria lacks specificity, with 90% of patients admitted to the ICU fulfilling two or more criteria.[1] However, this study challenges the concept the SIRS criteria is sensitive. The use of two SIRS criteria for the diagnosis of sepsis missed one person in every eight with severe sepsis. Although the mortality was lower in SIRS-negative patients, it was still substantial (9.3% in 2013). Furthermore, the linear increase in mortality seen with each additional SIRS criterion calls into question the wisdom of using an arbitrary cut off of two or or more SIRS criteria for the diagnosis of sepsis.

The strengths of the study are numerous; the dataset was large and was collected prospectively from 172 ICUs in the ANZICS group, meaning this study is likely to be applicable to the vast majority of ICU patients. There are subtleties in the data collection that warrant comment. The APACHE III diagnostic coding was not independently monitored. Patients were labelled as sepsis on admission to ICU. Firstly, it is unclear how many patients labelled as sepsis had positive microbiological results. Secondly, the presence of two or more SIRS criteria may have heightened clinical suspicion and have directly led to patients being coded as sepsis. In this regard, the SIRS criteria still may be positively contributing to patient care.

As this study used total white cell count only when looking for SIRS-positive severe sepsis, it did not take into account the presence of greater than 10% immature neutrophils as this data was not available.[2] 7,196 patients in the SIRS-negative severe

sepsis cohort fulfilled one SIRS criterion with a normal WCC. This may have led to some patients being incorrectly classified as SIRS-negative severe sepsis.[3] In data derived from patients with sepsis who met two or more SIRS criteria, Mare and colleagues found 22% of patients with normal WCC had greater than 10% immature neutrophils.[4] It is unclear how many patients this affected in this study.

For researchers this study also raises issues. Are patients with SIRS-negative severe sepsis both genotypically and phenotypically different from those with SIRS-positive severe sepsis? As such, should these patients be managed differently? How should we identify, and therefore recruit, this cohort of patients?

As physiological variables were only recorded intermittently, some patients may have been misclassified as SIRS-negative severe sepsis. The investigators comment that the use of data from the first 24 hours is a limitation of the study, as patients may move from being SIRS-negative to SIRS-positive as their illness progresses. Therefore, with time, the SIRS criteria may become more sensitive. The counter argument is the initial phase of sepsis is exactly where a sensitive test is required so appropriate treatment can be initiated.

The appreciable mortality of those in the SIRS-negative severe sepsis group, coupled with their higher than predicted mortality, creates concern for clinicians. A high index of suspicion must be maintained to identify and treat these 12% of patients. It is conceivable patients with SIRS-negative severe sepsis were identified later, and therefore received appropriate antibiotics later, adding to the higher than expected mortality. This adds weight to the argument that sepsis screening criteria need to be more sensitive.

Where it sits in the body of evidence

- In 1992 the American College of Chest Physicians and Society of Critical Care Medicine published definitions for SIRS. This included the presence of two or more of the following;
    - temperature > 38 °C or < 36 °C
    - heart rate > 90 beats per minute
    - respiratory rate > 20 breaths per minute, or $PaCO_2$ of less than 32 mmHg
    - WCC > 12,000 or < 4,000, or the presence of more than 10% immature neutrophils.[5]

- The EPIC II study was a 1-day, prospective, point prevalence study examining the demographic, physiological, bacteriological, therapeutic, and outcome data for patients with sepsis in 75 countries. Of the 13,796 patients for whom data were available, 51% were considered infected. Seventy one per cent of the total population were receiving antibiotics. Respiratory sepsis was the commonest cause (64%). Seventy

per cent of patients had positive culture results. The ICU mortality for infected patients was 25% compared to 11% of non-infected ICU patients.[6]

- In the first EPIC study, ICU-acquired infections were investigated using a point prevalence study. 10,038 patient case reports were examined. 2,064 patients (20.6%) had an ICU-acquired infection. Enterobacteriaceae (34.4%), Staphylococcus aureus (30.1% [of which 60% was MRSA]), Pseudomonas aeruginosa (28.7%), coagulase-negative staphylococci (19.1%), and fungi (17.1%) were the commonest organisms. Duration of ICU stay, indwelling catheters, ventilation and stress ulcer prophylaxis were identified as risk factors for ICU-acquired infection.[7]

- Martin and colleagues conducted an epidemiological study examining discharge data from 750 million hospital admissions over a 22 year period. Ten million episodes of sepsis were identified. Sepsis definitions were based on International Classification of Diseases diagnostic codes. Factors associated with increased risk of sepsis included being male (RR, 1.28; 95% CI, 1.24 to 1.32) and being non Caucasian (relative risk, 1.90; 95% CI, 1.81 to 2.00). In the period 1995 – 2000, one third of patients had at least one organ failure. Gram-positive bacteria was responsible for 52.1% of episodes of sepsis.[8]

- A retrospective analysis of 17,990 patients with severe sepsis and septic shock demonstrated that every hour antibiotics were delayed was associated with an increase in mortality.[9]

- Rivers and colleagues conducted a single-centre randomised controlled trial comparing early goal directed therapy (EGDT) with standard care in 263 patients with severe sepsis and septic shock. Patients in the EGDT group had a significantly lower in-hospital mortality (30.5%) compared with 46.5% in the standard care group (P = 0.009).[10]

- ProCESS was a randomised controlled trial conducted in 31 centres in the USA, involving 1,341 patients with septic shock. It compared three treatment strategies; EGDT, protocol-based standard therapy (which had resuscitation targets but did not mandate the use of a CVC and had lower thresholds for RBC transfusion than EGDT), and usual care. The primary endpoint of 60 day mortality occurred in 21.0% of the EGDT group, 18.2% of the protocol-based standard therapy and 18.9% of the usual care group. There was no statistical difference in mortality between the groups.[11]

- The ANZICS Clinical Trials Group conducted the ARISE trial, comparing EGDT with usual care in 51 ICUs in Australasia. This patient cohort had a lower APACHE II score (15.4 in the EGDT group) than the Rivers paper, ProMISe and ProCESS trials. There was no difference in 90-day mortality between the two groups (18.6% in the EGDT group vs 18.8% in the usual care group).[12]

- A meta-analysis of five trials which examined EGDT in sepsis was conducted. The five trials were ProMISe, ProCESS, ARISE, the original paper by Rivers and colleagues and a paper on lactate clearance by Jones and colleagues. There were 4,735 patients in the meta-analysis, with no difference in mortality between the EGDT group (23.2 %) and control group (22.4 %) (OR 1.01; 95 % CI, 0.88 to 1.16, P = 0.9). Further analysis of the ProMISe, ProCESS and ARISE trials (n = 4,063) demonstrated no difference in 90-day mortality (OR 0.99; 95 %, CI 0.86 to 1.15, P = 0.93).[13]

Should we implement this into our practice?
Yes (if you use SIRS). Few clinicians base their determination of the presence or absence of sepsis on the SIRS criteria. This study may have significant implications for epidemiological and therapeutic research, but little direct effect on clinical practice.

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Amato – Driving Pressure in ARDS

Amato MBP, Meade MO, Slutsky AS, Brochard L, Costa ELV, Schoenfeld DA, et al. Driving Pressure and Survival in the Acute Respiratory Distress Syndrome. New England Journal of Medicine. 2015 Feb 19;372(8):747–55.

Study synopsis

This post hoc analysis examines whether driving pressure (ΔP), measured as plateau pressure (Pplat) minus positive end expiratory pressure (PEEP), is more closely associated with survival than tidal volume (Vt) alone in patients with the acute respiratory distress syndrome (ARDS).

Data was used from nine previously conducted trials, involving a total of 3,562 patients, comparing different ventilation strategies in patients with ARDS. The investigators used a standard risk analysis with multivariable adjustments and a multilevel mediation analysis to examine the effect of a number of variables, including ΔP, on survival in ARDS. The primary end point was in hospital survival at 60-days.

Survival prediction models were derived, further modelled and validated from three separate cohorts. Data from 336 patients from four randomised controlled trials were used as a cohort to derive an initial survival prediction model. This model was further validated and refined when tested against data from 861 patients from the ARDSnet low tidal volume trial.[1] Finally, the model was validated against a cohort of 2,365 patients from four trials that examined the role of high versus low PEEP in ARDS.[2-5]

Variables examined included treatment group (e.g. lung protective ventilation) compared to control group, severity of illness (including APACHE, SAPS and PaO_2:FiO_2 ratio) and ventilation variables (e.g. Vt and Pplat).

To examine the prognostic significance of ΔP in the derivation and validation analysis, patients with matched levels of PEEP, but different levels of ΔP, were compared. Mediation analysis was used to test which of four variables: Vt, Pplat, PEEP, and ΔP best explained the survival benefit seen in treatment groups.

Driving pressure was strongly associated with survival in all three cohorts from which the survival prediction model was derived, refined and validated. A one standard deviation increase in ΔP (equating to 7 cmH_2O) measured at day 1 was associated with increased mortality. The relative risk for mortality was 1.50 (95% CI, 1.34 - 1.68, $P < 0.001$) in the high versus low PEEP cohort (n = 2365) and 1.41 (95% CI, 1.32 - 1.52, $P < 0.001$) in the combined cohort (n = 3562). No other ventilation variable (VT, Pplat or PEEP) had a statistically significant impact on survival.

When examining the role of ΔP, PEEP, and plateau pressures on survival, the following was seen;

- if ΔP was constant and high plateau pressures were as a result of high PEEP, then no increase in mortality was seen (P = 0.61)
- if PEEP was constant and high plateau pressures were as a result of high ΔP, then an increase in mortality was seen (P < 0.001)
- if Pplat was constant; increasing PEEP and therefore decreasing ΔP was associated with an increase in survival (P < 0.001)

Patients who received only lung protective ventilation were analysed (Pplat ≤ 30 cmH_2O and Vt ≤ 7 mL/kg ideal body weight). Those who had a ΔP ≤ median (13 cmH_2O) had an improved survival compared with those with driving pressure > 13 cmH_2O (RR, 1.36; 95% CI, 1.17 to 1.58; P < 0.001). In mediation analysis, ΔP was responsible for 75% of the treatment benefit seen in the tidal volume trials (P = 0.004) and 45% of the benefits seen in the PEEP trials (P = 0.001).

Critique

Despite being a post hoc analysis, this was an intriguing study which raises many questions about ventilatory management. Previous studies in ARDS have used Vt corrected for ideal body weight to limit volutrauma and barotrauma. The investigators argue this strategy fails to fully take into account the actual volume of lung being ventilated and therefore the respiratory system compliance (CRS).

In the original ARDSnet low tidal volume study, patients allocated to the low Vt group had an initial Vt of 6 ml/kg, but this could be reduced to a minimum of 4 ml/kg if Pplat remained above 30 cmH_20. Therefore, some attempt was made to adjust for compliance. Driving pressure is a means of normalising Vt for respiratory system compliance (ΔP = Vt/CRS). In the revised Berlin definition of ARDS, CRS was noted to be one of the markers of disease severity, and so ΔP is is determined by factors know to predict mortality.[6,7] Driving pressure corrects for the volume of lung actually being ventilated in ARDS. As such, it is biologically plausible that reductions in Vt are only associated with improved survival if there is a commensurate decrease in driving pressure.

This study raises an important clinical question; which component of lung protective ventilation has the greatest effect on outcomes? The relationships between ΔP, PEEP and Pplat are complex. Inadequate PEEP will result in atelectrauma due to cyclical collapse and re-expansion of alveolar lung units. Appropriate use of PEEP will result in improved respiratory system compliance. In everyday practice clinicians are faced with the dilemma of increasing PEEP at the expense of higher plateau pressures. It would seem from this study this may not be harmful.

The relationship between ΔP and PEEP is noteworthy. The mediation analysis suggests

ΔP had a larger impact on outcomes in the Vt trials than the high PEEP trials. This may represent one of two possibilities. Firstly, the effect of ΔP on mortality is reduced when high PEEP is used, possibly as a result of less atelectrauma. Contrary to this argument is the finding that mortality is unaltered when PEEP is increased, but ΔP is unchanged. Secondly, this could represent a flaw in the prediction model.

That ΔP consistently predicted survival across a range of data sets derived from studies published from 1998 - 2008 lends strength to the argument it may be the major mediator of the treatment benefit seen in lung protective ventilation. The survival benefits seen with lung protective ventilation are likely mediated by a reduction in the inflammatory cascade created by barotrauma, volutrauma and atelectrauma. This serves to remind clinicians that ARDS has multi system effects.

This study did not examine the effect of ΔP on patients on pressure support ventilation, or those with spontaneous respiratory effort, as they were excluded from this study. However, this only accounted for 3% of the study population.

The primary end point was in hospital 60-day mortality, with patients discharged before 60-days were censured and assumed to be alive. 3,562 patients were involved in the initial nine studies, however, only 3,080 were involved in the cox regression module. It is unclear how many were censured due to discharge.

The major limitation of this study is, as a post hoc observational analysis, it does not prove causality. The previous trials from which the datasets were taken were not designed to assess ΔP as an independent variable. This study will doubtless form the basis for future trials. The associated editorial points out planning a trial of ΔP will prove difficult, especially in relation to carbon dioxide removal and the complex relationship with PEEP.[7] Whether a measured variable such as ΔP translates into a successful therapy for treating ARDS remains to be seen. Until that time, this paper stands alone as an interesting study examining a survival prediction model.

Where it sits in the body of evidence

- The ARDSnet group conducted a trial comparing lung protective ventilation (Vt 6 ml/kg predicted ideal body weight and Pplat < 30 cmH_2O) with conventional ventilation (Vt 12ml/kg predicted ideal body weight and Pplat < 50 cmH_2O). Patients managed with lung protective ventilation had a lower mortality (31.0%) than those managed with conventional ventilation (39.8%) (P = 0.007). Long protective ventilation also resulted in a greater number of ventilator free days in the first 28 days after randomisation 12 +/- 11 vs. 10 +/- 11 (P = 0.007).[1] The major criticism of this paper related to the large tidal volumes used in the control group.

- 549 patients with ARDS (PaO_2:FiO_2 ratio < 300 mmHg) were recruited into a trial

comparing high versus low PEEP, in addition to lung protective ventilation. Mean PEEP values were 8.3 ± 3.2 cmH_2O in the low PEEP group compared to 13.2 ± 3.5 cmH_2O in the higher-PEEP group (P < 0.001). In hospital mortality was 24.9% and 27.5% respectively (P = 0.48).[3]

- A meta-analysis examining the effect of PEEP on mortality in patients with ARDS found high PEEP (in conjunction with lung protective ventilation) to be beneficial in patients with a PaO_2:FiO_2 ratio < 200 mmHg. The in-hospital mortality was 34.1% in the high PEEP group vs. 39.1% in the low PEEP group (adjusted relative risk, 0.90; 95% CI, 0.81 to 1.00, P = 0.049). In patients with a PaO_2:FiO_2 200 - 300 mmHg, in-hospital mortality was 27.2% in the high PEEP group vs. 19.4% in the low PEEP group (adjusted RR, 1.37; 95% CI, 0.98 to 1.92, P = 0.07).[8]

- The PROSEVA study examined prone positioning for 16 hours per day in patients with ARDS and a PaO_2:FiO_2 of < 150 mmHg. The 28-day mortality was significantly lower in the prone group 16.0% vs 32.8% (P < 0.001) (hazard ratio for death, 0.39; 95% CI, 0.25 to 0.63).[9]

- A trial of lung protective ventilation in patients without lung injury compared ventilation with 10 ml/kg (conventional ventilation group) with 6 ml/kg (lung protective group) based on predicted body weight. 13.5% of the conventional ventilation group went on to develop ARDS compared to 2.6% in the lung protective group (P = 0.01).[10]

- A multi-centre trial examined the effect of protective ventilation (Vt 6 - 8 ml/kg of predicted body weight, PEEP 6 - 8 cmH_2O, and recruitment manoeuvres every 30 minutes) vs non-protective ventilation (Vt 10 - 12 ml/kg of predicted body weight, no PEEP and no recruitment manoeuvres) in patients undergoing major abdominal surgery. Patients were recruited if they were at intermediate or high risk of respiratory complications in the post operative period. 17.5% of patients in the protective-ventilation group developed a pulmonary complication in the first 7 days, compared to 36.0% in the non protective-ventilation group (adjusted RR, 0.49; 95% CI, 0.32 to 0.74, P < 0.001).[11]

- The use of high frequency oscillatory ventilation (HFOV) was compared to lung protective ventilation in patients with ARDS and a PaO_2:FiO_2 < 200 mmHg. HFOV was associated with a higher in-hospital mortality (47%) than the control group (35%) (RR of death with HFOV, 1.33; 95% CI, 1.09 to 1.64, P = 0.005).[12]

- The Berlin definition of ARDS examined mortality prediction using PaO_2:FiO_2 ≤ 100 mmHg alone versus PaO_2:FiO_2 ≤ 100 mmHg plus four ancillary variables (radiographic severity, respiratory system compliance (≤ 40 mL/cmH_2O), positive end-expiratory

pressure (≥ 10 cmH_2O), and corrected expired volume per minute (≥10 L/min). The addition of these four ancillary variables did not improve the ability to predict mortality.[6]

Should we implement this into our practice?
Maybe. This needs a randomised controlled trial investigating driving pressure to correctly determine the consequences of controlling this variable. In the interim, it may be prudent to limit driving pressure to less than 13 cmH_20 when possible.

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The 3Sites Study

Parienti J, Mongardon N, Mégarbane B, Mira J, Kalfon P, Gros A, et al. Intravascular Complications of Central Venous Catheterization by Insertion Site. New England Journal of Medicine. 2015 Sept 24; 373; 13:1220-9.

Study synopsis

This was a multi-centre, randomised trial performed in ten intensive care units in France. Its primary aim was to investigate the incidence of catheter-related bloodstream infection and symptomatic deep-vein thrombosis related to the main sites of central line insertion, namely the subclavian, internal jugular and femoral veins.

Patients admitted to the adult intensive care unit who required a new central line and were deemed by the treating physician to have more than one site available for central access were eligible for recruitment. Randomisation occurred via a centralised 24 hour web or phone based system. Patients were randomised in a 1:1:1 scheme if all three sites were available for insertion, if only two sites were available the scheme randomised on a 1:1 basis. The randomisation process was also stratified for each intensive care unit and whether the patient was on antibiotics.

The central line insertion was performed in compliance with international guidelines by a physician with a minimum of 50 central line insertions using full sterile barrier precautions.[1,2] A Seldinger insertion technique was used and ultrasound or landmark techniques were allowed. None of the study catheters were antiseptic impregnated, antibiotic-impregnated, or tunnelled. Infective complications were sought by quantitative culture of the line tip after aseptic removal and simultaneous peripheral culture or by simultaneous culture from a peripheral vein and the central venous catheter to determine the differential time to positivity if the line remained in situ at ICU discharge. Thrombotic complications were assessed within 48 hours of catheter removal by compression ultrasonography to confirm symptomatic catheter-related deep-vein thrombosis and to detect asymptomatic deep-vein thrombosis.

The primary outcome of this study was a composite of catheter related blood stream infections and symptomatic deep vein thrombosis. A diagnosis of catheter-related bloodstream infection required catheter-tip colonization with the same phenotypic micro-organism isolated from the peripheral blood culture; if the organism was a potential skin contaminant then two peripheral cultures were required. Deep vein thrombosis was suspected if the patient had any symptoms potentially related to a clot and confirmation was sought with ultrasonography. Secondary outcomes were the incidence of predefined mechanical complications of central line insertion.

The sample size calculation was based on major catheter-related complications between

jugular and subclavian cannulation. A sample size per arm to achieve a power of 0.85 and a two-sided alpha of 0.05 was 813 in the 3-choice group. The authors subsequently estimated that 3,333 catheter insertions were required. Analyses were performed using the intention-to-treat principle. The incidence of the primary outcome was compared among the three insertion sites in the three-choice comparison, with the use of the overall log-rank test, while pairwise comparisons were conducted combining groups from the three-choice scheme with the relevant groups from the two-choice scheme using a cox model.

A total of 3,471 catheters in 3,027 patients (1,284 jugular, 1,171 femoral, and 1,016 subclavian) were included, of which 2,532 (72.9%) were randomly assigned in the three choice scheme (845 jugular, 844 femoral, and 843 subclavian). Baseline characteristics were similar in the three groups. The median duration of catheter insertion was 5 days for each of the three insertion sites.

In the three-choice comparison, there were 50 primary outcome events, with 8 events in the subclavian group, 20 events in the jugular group, and 22 events in the femoral group (1.5, 3.6, and 4.6 per 1000 catheter-days (P = 0.02). In pairwise comparisons for the primary outcome, the risk of the primary outcome was significantly higher in the femoral group than in the subclavian group (HR, 3.5; 95% CI, 1.5 to 7.8; P = 0.003) and in the jugular group than in the subclavian group (HR, 2.1; 95% CI, 1.0 to 4.3; P = 0.04), whereas the risk in the femoral group was similar to that in the jugular group (HR, 1.3; 95% CI, 0.8 to 2.1; P = 0.30). For rates of mechanical complications during insertion, there were significantly more events in the subclavian site compared to jugular and femoral sites (2.1%, 1.4% and 0.7% respectively); almost exclusively pneumothoraces.

Critique

Central venous catheter (CVC) insertion is a common, often essential, procedure performed in the intensive care unit to allow administration of inotropes and other medications. However, insertion is associated with both mechanical and infectious complications, which may increase morbidity and mortality.[3-5] There are a number of factors identified in international guidelines which may affect the subsequent catheter infection rates, including hand hygiene, disinfection of the skin, use of catheters coated with antimicrobial or antiseptic agents, catheter dressings and insertion site.[6,7] In terms of insertion site, previous observational studies have found similar risks of infection between the subclavian, femoral and jugular sites.[8,9] Conversely, two randomised trials have compared the subclavian with femoral[10] and jugular with femoral[11] sites, with both finding the femoral site was associated with a higher infection risk. A previous meta analysis has suggested the subclavian site is associated with less infection risk, however, there has been no direct comparison in a randomised trial of subclavian, jugular and femoral sites.[12] This trial was therefore important in our understanding of insertion site choice and risk of complications.

This study has multiple strengths. It is the largest randomised multi-centre trial investigating complications of all three central venous catheter insertion sites. The power calculation is complicated and based on both multiple previous studies and on an exponential model of complications over time. The infection rates in the study were lower than that used in the power calculation, however, the median insertion times were also shorter. Regardless, in terms of catheter numbers, this is still an impressive trial. The randomisation process was also effective, ensuring an adequate distribution of sites. Stratification during randomisation by both intensive care unit and antibiotic use reduced potential confounders. In terms of the insertion of lines, the investigators also aimed to standardise the procedure across sites, using published guidelines for prevention of infection. Operators also had to have considerable experience in line insertion at all three sites (>50 insertions). The diagnosis of catheter-related blood stream infection can be difficult and there are multiple techniques described. Another strength of this trial is that the quantitative technique used has been recommended by international guidelines[13] and meta-analysis.[14] There were no patients lost to follow up and loss of data was generally low (2.9%). Finally, the use of external, independent clinical monitors who validated a randomly selected 12% of the data, and all primary and secondary outcomes, adds the robustness of the trial.

There are some limitations however. Site selection was at the discretion of the investigators, who were unblinded. However, the reason for exclusion of sites had to be documented and these were clinically relevant issues, such as site contamination or avoidance of a pneumothorax in severe respiratory failure. This issue is probably negated by the even distribution between the three site groups. In terms of the actual catheter insertion, although it was attempted to standardise the procedure, ultrasound was not mandatory. Clinicians were encouraged to use ultrasound for catheter insertion, this was not compulsory. Ultrasound insertion for all three sites have generally been shown to improve success and reduce mechanical complications.[15-19] However, it is less clear if ultrasound has an effect on infectious complications.[20] There was also a significant failure rate in the subclavian group (14.7%), although the trial design and intention-to-treat basis will have compensated for this problem. Another variable was the choice of skin disinfectant, with alcohol-based solutions mainly used, but some centres using chlorhexidine. The distribution of cleaning solutions was relatively even however, despite chlorhexidine with alcohol being recommended by some guidelines.[6] Finally, this study had a relatively short follow up period, effectively while the patient was in ICU. Subsequently, patients who had catheters remaining in situ had a different (although still approved) diagnostic approach to infectious complications and also were not followed up for asymptomatic venous thrombosis. It is unclear if these changes significantly affected the results. The investigators state as over half the data on asymptomatic venous thrombosis was not available, the total incidence of thrombosis should be interpreted with caution.

It was concluded catheterisation of the subclavian vein was associated with a lower risk of the composite outcome of catheter-related bloodstream infection and symptomatic deep-vein thrombosis than that associated with the jugular vein or femoral vein, but with a high risk of mechanical complications. With diagnostic issues with venous thrombosis, perhaps the primary outcome should have been infectious complications alone.

Where it sits in the body of evidence

- In a prospective observation multi-centre study to determine the rate of complications with vascular catheters in the ICU, 503 central catheters were inserted (jugular 114, subclavian 194, femoral 69, others 126).[21] Culture of the vascular-catheter tip was positive for 24% of central catheters (32 of 1,000 catheters days). There were positive tip cultures in 40 jugular, 28 subclavian and 13 femoral lines. Three factors, duration of catheterisation (OR, 2.5; 95% CI, 1.2 to 5.3; P < 0.05), use of a semi-permeable transparent dressing (OR, 2.8; 95% CI, 1.1 to 7.4 P < 0.05), and the jugular insertion site (OR, 2.7; 95% CI, 1.0 to 7.5; P < 0.05), were found to be independently associated with positive cultures of central catheters by multivariate analysis.

- In a study investigating the pathogenesis of pulmonary artery catheter infection in a mixed ICU population, cultures were performed from multiple sources on the patient and the catheter parts.[22] Overall, 65 (22%) of 297 Swan-Ganz catheters showed local infection of the introducer (58 catheters) or the intravascular portion of the PA catheter (20 catheters); only two catheters (0.7%) caused bacteraemia. Cutaneous colonization of the insertion site with greater than 10^2 cfu/10 cm^2 (RR 5.5; p< 0.001), insertion into an internal jugular vein (RR 4.3; p < 0.01), catheterisation greater than 3 days (RR 3.1; p < 0.01), and insertion in the operating room using less stringent barrier precautions (RR 2.1; p = 0.03) were each associated with a significantly increased risk of catheter-related infection.

- A randomised trial investigating the use of antimicrobial impregnated central venous lines in a surgical critical care randomised 306 patients to impregnated versus standard central venous lines.[23] The main findings were that coated catheters were effective in reducing the rate of significant bacterial growth on either the tip or intradermal segment (40%) compared with control catheters (52%; P = 0.04) without an effect on bacteraemias. However, variables that were associated with a significant amount of growth on the tip or intradermal segment were duration of catheterisation of longer than 7 days, jugular insertion site, and the absence of a CSS coating.

- A prospective observational study of all non-tunnelled central venous catheters over 28-months to determine the influence of catheter site and type (single- vs triple-lumen) on infection was performed on hospital wards.[24] End-points were clinical

infection and catheter contamination. Three hundred catheters were inserted. Seventy percent were inserted into upper-body sites, and 30% were inserted into the femoral vein. Forty-five percent were triple-lumen catheters. Bacteraemia occurred in 2.7% of insertions; insertion-site infections developed in 1.3%, and catheter colonization developed in 12%. Catheter contamination was associated with emergency insertion (OR, 6.2; 95% CI, 1.1 to 36.7; P = 0.04) by logistic regression and with femoral location (HR, 4.2; 95% CI; 2.0 to 8.8; P = 0.0001) by Cox regression. Clinical infection was not associated with any of the risk factors evaluated.

- A concealed, controlled trial conducted at 8 ICUs in France randomised 289 patients to either femoral (n = 145) or subclavian (n = 144) catheterisation to compare mechanical, infectious, and thrombotic complications.[10] Femoral catheterisation was associated with a higher incidence rate of overall infectious complications (19.8% vs 4.5%; P < 0.001; incidence density of 20 vs 3.7 per 1,000 catheter-days) and of major infectious complications (clinical sepsis with or without bloodstream infection, 4.4% vs 1.5%; P = 0.07; incidence density of 4.5 vs 1.2 per 1,000 catheter-days), as well as of overall thrombotic complications (21.5% vs 1.9%; P < 0.001). Major mechanical complications were similar between the 2 groups (17.3% vs 18.8 %; P = 0.74 and 1.4% vs 2.8%; P = 0.44, respectively). The only factor associated with infectious complications was femoral catheterisation (HR, 4.83; 95% CI, 1.96 to 11.93; P < 0.001).

- Five hundred and thirty-nine patients were enrolled In a multi-centre randomized, controlled trial, testing the effectiveness of an antimicrobial central venous catheter.[25] Catheters were mainly inserted into the jugular and subclavian vessels. There was no significant difference in the primary outcome of colonization or bacteraemia rates between the test and control catheters. However, there were significant differences in colonization rates; right internal jugular (31%), subclavian sites (left 15%; right 27%) were significantly below (P < 0.05) that for the left internal jugular site (53%). Multivariate logistic regression analysis confirmed insertion site and dressing change frequency contributed independently to the risk of colonization. Specifically, the odds ratio for subclavian compared with internal jugular was 0.45 (95% CI, 0.29 to 0.70).

- In a single-centre observational study in a mixed ICU, the rates of positive quantitative culture (PQC) of arterial catheter (AC) and central venous catheter (CVC) tips and of CVC- and AC-related bacteraemia were examined.[26] A PQC was defined by a catheter tip culture yielding ≥ 10^3 colony forming units (cfu)/mL. The analysis included 308 CVCs (160 jugular, 92 subclavian and 56 femoral) and 299 arterial catheters. The cumulative incidence (PQCs/number of catheters inserted) was 9.4% (29/308) for CVCs and 7.7% (23/299) for ACs (P = 0.44). Incidence density (PQCs/1,000 catheter days) was 12.0 for CVCs versus 9.3 for ACs. The rate of PQC was greater with internal jugular or femoral vein catheters than with those placed via the subclavian route (relative risk, 3.6 vs. 3.8;

95% CI, 1.1 to 12 vs. 1.03 to 14.2; P < 0.02 vs. P < 0 .03).

- In a prospective observational study to assess the risk of central venous catheter infection with respect to the site of insertion in an ICU population, a total of 831 central venous catheters and 4,735 catheter days in 657 patients were studied.[8] The incidence of catheter infection (4.01/1,000 catheter days, 2.29% of catheters) and colonization (5.07/1,000 catheter days, 2.89% of catheters) was low overall. In group 1, the incidence of infection was subclavian, 0.881 infections/1,000 catheter days (0.45%), internal jugular, 0/1,000 (0%), and femoral, 2.98/1,000 (1.44%; P = 0.2635). The incidence of colonization was subclavian, 0.881 colonization/1,000 catheter days (0.45%), internal jugular, 2.00/1,000 (1.05%), and femoral, 5.96/1,000 (2.88%, P = 0.1338). There were no statistically significant differences in the incidence of infection and colonization or duration of catheters (P = 0.8907) among the insertion sites.

- In another observation study across an entire hospital examining positive line cultures, 806 central venous catheters were recorded.[27] The rate of positive cultures was 7.1%, and complications other than infection occurred in 0.5%. Infection rates were 3.8 per 1,000 catheter-days in subclavian, 6.1 in jugular, and 15.7 in femoral vein catheterisation, respectively. In high-risk departments (ICUs and emergency departments) the infection rate was 5.4 for subclavian and 10.2 for jugular catheterisation, whereas it was 3.6 for subclavian and 4.6 for jugular catheterisation in non critical care departments.

- In a 2 year prospective, single-centre, observational study, comparing colonisation and catheter-related bloodstream infection (CR-BSI) rates among three insertion sites, 605 CVCs (4,040 catheter days) were analysed.[9] Colonisation and CR-BSI incidence were, respectively, 15.1 (95% CI, 13.5 to 21.0) and 1.8 (95% CI 1.2 to 4.2) per 1,000 catheter-days. Colonisation was higher at the internal jugular (HR 3.64; 95% CI 1.32 to 10.00; P = 0.01) and femoral (HR 5.15; 95% CI, 1.82 to 14.51; p=0.004) sites than at the subclavian site. No difference in CR-BSI rates was noted between the three sites.

- In a concealed, randomized, multi-centre, evaluator-blinded, parallel-group trial (the Cathedia Study), 750 patients were randomized to receive jugular or femoral vein catheterisation by experienced operators.[11] Catheter colonization on removal (primary end point), and catheter-related bloodstream infection were examined. The risk of catheter colonization at removal did not differ significantly between the femoral and jugular groups (incidence of 40.8 vs 35.7 per 1000 catheter-days; HR, 0.85; 95% CI, 0.62 to 1.16; P = 0.31). Although when body mass index was accounted for, the jugular site appeared worse in normal to low BMI but superior in higher BMI patients. Rates of catheter-related bloodstream infections were similar. For mechanical complications, more haematomas occurred in the jugular group than in the femoral group (13/366

patients [3.6%] vs 4/370 patients [1.1%], respectively; P = 0.03).

Should we implement this into our practice?
Possibly, although the overall patient-centred effect of a combined profile of reduced infectious complications but higher mechanical complications was not determined. The findings of this study are consistent with prior studies. Perhaps the use of ultrasound may indirectly reduce the risk of infection by facilitating mechanically uncomplicated subclavian placement.

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The STOPAH Trial

Thursz MR, Richardson P, Allison M, Austin A, Bowers M, Day CP et al. Prednisolone or Pentoxifylline for Alcoholic Hepatitis. New England Journal of Medicine 2015 Apr 25; 372; 17: 1619-28.

Study synopsis

This was a was a multi-centre, randomised, double-blind trial with a 2-by-2 factorial design performed across 65 hospitals in the United Kingdom. The primary aim was to investigate the effect on mortality of prednisolone and pentoxifylline, either alone or in combination, in acute severe alcoholic hepatitis.

Adult patients who were admitted to hospital with a clinical diagnosis of alcoholic hepatitis, a history of recent excess alcohol consumption (men > 80g/day, women > 60 g/day), a bilirubin > 80 µmol/L, and a Maddrey Discriminant Function > 32 were eligible for recruitment. Patients were excluded if they had prolonged jaundice (> 3 months), cessation of alcohol (> 2 months), another cause of liver disease and elevated AST > 500 IU/L or ALT > 300 IU/L. Patients with renal failure or who required renal replacement therapy, had active GI bleeding, sepsis or a need for inotropes were also excluded unless they improved in the first seven days.

Recruited patients were randomized using a web based system to one of four groups, with one group receiving placebo only, the second group receiving prednisolone 40 mg daily plus placebo, the third group receiving pentoxifylline 400 mg three times daily plus placebo, and the fourth group receiving prednisolone 40 mg daily and pentoxifylline 400 mg three times daily. All treatments were for 28 days. All other treatments were at the discretion of the treating physician. The randomisation was also stratified according to region and defined patient risk.

The primary end point was mortality at 28-days. Secondary end points included mortality or liver transplantation at 90-days and at 1 year The sample size calculation was based on a 28-day mortality of 30%, with an absolute reduction of 9% with treatment. An estimated 1,026 patients were required to achieve a 90% power at significance level of 0.05. The target recruitment was set at 1,200 allowing for a 10% loss. Analysis was based on the intention-to-treat principle for primary end points.

A total of 5,234 patients were screened and subsequently 1,103 patients were randomised to the four treatment groups. Baseline characteristics were well matched, in particular prothrombin times, serum bilirubin and albumin levels. Prognostic scoring systems results were similar. Time to enrolment averaged 6 days. There were some patients with sepsis (10%) and GI bleeding (6%) who were stabilised and then recruited.

There was no statistical difference in the primary outcome of mortality at 28-days in any group (P = 0.41), 17% in the placebo–placebo group, 14% in the prednisolone–placebo group, 19% in the pentoxifylline–placebo group, and 13% in the prednisolone–pentoxifylline group. In a predefined logistic regression, adjusting for risk category and factorial design, there was again no statistically significant difference with either prednisolone 0.72 (95% CI, 0.52 to 1.01; P = 0.06) or pentoxifylline 1.07 (95% CI, 0.77 to 1.49; P = 0.69) treatment.

In a multivariate analyses, age, encephalopathy, white cell count, prothrombin ratio, and serum levels of bilirubin, creatinine, and urea were found to influence mortality. Subsequently, in a secondary analysis, in which a multivariate logistic-regression model was used to adjust for these variables, the odds ratio for 28-day mortality among the patients who received prednisolone, was 0.61 (95% CI, 0.41 to 0.91; P = 0.02). However, this effect was not continued to 90-days or 1 year. Prednisolone was associated with increased risk of infection, 13% vs 7% (P = 0.002).

Critique

Alcoholic hepatitis is a clinical syndrome observed in individuals who actively and chronically abuse alcohol. The syndrome is marked by jaundice, a serum bilirubin level above 80 µmol/L, and functional liver impairment. The condition has a potentially high short and long term mortality[1] and any treatment advances are therefore of major relevance. Guidelines on the management of alcoholic liver disease from the European Association for the Study of the Liver[2] and the American Association for the Study of Liver Diseases,[3] cite prednisolone and the oral phosphodiesterase inhibitor pentoxifylline as treatment options. However, these treatments are controversial. A Cochrane review[4] of 15 randomized trials comparing glucocorticoids with placebo reported no significant effect; however, a subsequent reanalysis[5] of the five largest studies indicated a significant mortality benefit. There is also a lack of convincing evidence for pentoxifylline. One trial[6] reported a benefit in severe disease, but again meta analysis[7] has not confirmed these findings. Comparisons of the two drugs have not added clarity,[7,8] while the combination of the two did not seem to confer benefit.[9,10] Therefore, a large trial with placebo, single and combination therapy could be justified.

This study has multiple strengths. It is the largest randomised multi-centre therapeutic trial in patients with alcoholic hepatitis. An appropriate power calculation was performed based on the mortality findings from previous studies. Statistical methodology was sound and analysis was performed on an intention-to-treat basis. The trial enrolled an adequate number of patients and the randomisation produced groups with similar baseline characteristics. The patients and clinicians were blinded in an appropriate manner, with all patients receiving the same amount of tablets per day. The follow up of patients in a potentially difficult group was to be commended and this is despite the trial stopping before complete follow up periods for 90 day (33 patients) and

1 year (159 patients) analyses.

As ever, there are some limitations. A major problem was the trial mortality; overall 28-day mortality was 16%, which was significantly lower than expected and upon which the power calculation was based. The power of the study was thus reduced and with the possibility the trial was not large enough to demonstrate a treatment effect. Furthermore, that the trial was only able to demonstrate a statistically significant result in favour of prednisolone after extensive multivariate post-hoc analysis adds to the uncertainty of any clinical benefit.

The trial screened a large number of patients, but excluded 79%, with almost half of the exclusions being because patients had a lower bilirubin or Maddrey's discriminant function. Both these variable eliminated potentially less severe disease and could actually be considered beneficial, as more severe cases may be expected to show a greater treatment effect. However, the inclusion and exclusion criteria could be criticised for a number of reasons. Firstly, the inclusion criteria used a clinical diagnosis of alcoholic hepatitis, rather than histological. Clearly, this is a pragmatic approach and reflective of real world practice, as not every patient with suspected alcoholic hepatitis is biopsied. Secondly, and of particular relevance to critical care, was the exclusion of patients with severe kidney injury, sepsis, GI bleeding or hypotension. Although some of these patients were randomised, this excluded 161 patients. This limits generalisability to the population of patients requiring critical care.

The investigators conclude that pentoxifylline did not improve outcomes in patients with alcoholic hepatitis, but the findings suggest the administration of 40 mg of prednisolone daily for 1 month may have a beneficial effect on short term mortality. However, the primary question has still has not been adequately answered.

Where it sits in the body of evidence

- There are multiple trials investigating the role of oral prednisolone therapy in alcoholic hepatitis, with earlier trials using variable doses and duration of treatment. Below are the more recent trials which used similar prednisolone doses.

- An early randomised, double blind study, including 55 patients with severe alcoholic hepatitis, compared prednisolone (40 mg per day) with placebo for 30 days.[1] Mortality in the placebo group was 13% versus 4% in the steroid group. Only after secondary analysis did the corticosteroid therapy show significance.

- In a similar small randomised trial with 28 patients who received prednisolone 40 mg for 28 days, with a tapering dose over a further two weeks, there was no observed benefit with steroid therapy.[11]

- A larger trial with both moderate and severe alcoholic hepatitis, randomly assigned 263 patients to one of three treatments: prednisolone, oxandrolone, or placebo for 30 days.[12] Short term 30-day mortality in the groups receiving steroid therapy was not significantly different from the placebo group. Thirteen per cent of the moderately ill patients and 29 per cent of the severely ill patients died. Although neither steroid improved short-term survival, oxandrolone therapy was associated with a beneficial effect on long-term survival. The conditional six-month mortality was 3.5 % after oxandrolone and 19% after placebo (P = 0.02). Prednisolone had no observed effect.

- In contrast, in a double blind, randomised controlled trial, 28 days of prednisolone treatment (40 mg per day) was compared with placebo in 61 patients with biopsy proven severe alcoholic hepatitis.[13] By the 66th day after randomization, 16 of 29 placebo recipients had died (mean [SE] survival, 45 [±8] %), as compared with 4 of 32 prednisolone recipients (88 ± 5 %) (log-rank test, 10.9; P = 0.001).

- The use of pentoxifylline, an inhibitor of tumour necrosis factor (TNF), has been less widely studied. In the largest of these trials, 101 patients with severe alcoholic hepatitis were randomized to pentoxifylline (400 mg orally 3 times daily) or placebo.[5] The primary endpoints of the study were the effect of pentoxifylline on survival and progression to hepatorenal syndrome. Twelve (24.5%) of the 49 patients who received pentoxifylline and 24 (46.1%) of the 52 patients who received placebo died (P = 0.037; RR, 0.59; 95% CI, 0.35 to 0.97). Hepatorenal syndrome was the cause of death in 6 (50%) and 22 (91.7%) patients (RR, 0.29; 95% CI, 0.13 to 0.65; P = 0.009). The trial concluded that treatment with pentoxifylline improves short-term survival in patients with severe alcoholic hepatitis due to reduction in hepatorenal syndrome.

- In a small randomised trial of 50 patients with severe alcoholic hepatitis, twenty five patients were randomised to receive pentoxifylline (400 mg orally, three times a day), and 25 received placebo for 4 weeks.[14] At 4 weeks, the patients treated with pentoxifylline showed significant differences in creatinine (P < 0.002), prothrombin time (P < 0.006), and TNF (P < 0.007), compared with placebo. Mortality in the pentoxifylline group was lower than in controls 20% (5/25) versus 40% (10/25) respectively, but this failed to reach significance; (RR, 0.5; 95% CI, 0.19 to 1.25; P = 0.216).

- In a similar trial with identical enrolment criteria, 30 patients were randomised to receive either pentoxifylline (14 patients) or placebo (16 patients) for 4 weeks.[15] This trial failed to show a significant effect. Four (28.57%) treated and seven (43.75%) control patients died (P = 0.09). Of the patients who died, renal failure developed in 2 (50%) pentoxifylline treated and 6 (85.7%) control patients (P = 0.1).

- Finally, there are several trials comparing prednisolone and pentoxifylline, and then the addition of pentoxifylline to prednisolone against the steroid alone.

- In a small randomised trial, 68 patients with severe alcoholic hepatitis were treated for 28 days with either pentoxifylline or prednisolone.[8] The probability of dying at the end of 3 months was higher in prednisolone group as compared to pentoxifylline (35.29% vs 14.71%, P = 0.04; log rank test). MELD score at day-28 of therapy was also significantly lower in the pentoxifylline group (15.53 ± 3.63 vs 17.78 ± 4.56, P = 0.04).

- In another multi-centre, open-labelled trial, 121 patients with severe alcoholic hepatitis were randomised to receive pentoxifylline (400 mg, 3 times daily) or prednisolone (40 mg daily) in a non-inferiority study.[7] The 1-month and 6-month survival rates were not significantly different, nor was there a difference in complication rates. However at 7 days, the response to therapy assessed by the Lille model favoured prednisolone 0.35 vs. 0.50 (p = 0.012).

- Seventy patients with severe alcoholic hepatitis were randomised to treatment for four weeks with either prednisolone 40 mg/day plus pentoxifylline 400 mg thrice/day (n = 36) or prednisolone 40 mg/day alone (n = 34).[10] Patients were followed up for 6 months. Four-week and six-month survival were not significantly different (four-week, 72.2 and 73.5%, respectively; P = 1.00; six-month, 30.6 and 23.5%, respectively; P = 0.417). There were no other benefits observed with the addition of pentoxifylline.

- In a further multi-centre, double-blind clinical trial, 270 patients with severe biopsy-proven alcoholic hepatitis were randomised to an identical treatment regime.[9] Six month survival was not different between the pentoxifylline-prednisolone and placebo-prednisolone groups (69.9% [95% CI, 62.1% to 77.7%] vs 69.2% [95% CI, 61.4% to 76.9%], P = 0.91). Again, there were no other significant findings, although hepatorenal syndrome occurred less in the group with additional pentoxifylline treatment.

- Finally, in a smaller study, a total of 60 patients, 30 in each group, were randomised to either pentoxifylline with prednisolone or pentoxifylline alone.[16] There was no benefit from this combination therapy versus pentoxifylline alone.

Should we implement this into our practice?

Not based on this study, as it effectively excludes critically ill patients. This trial suggests pentoxifylline 400mg daily for 28 days has no benefit, whilst prednisolone 40mg daily for 28 days may be beneficial for short-term outcomes, but not for medium or long-term outcomes.

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Paul - Cotrimoxazole vs. Vancomycin for severe MRSA Infection

Paul M, Bishara J, Yahav D, Goldberg E, Neuberger A, Ghanem-Zoubi N, et al. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin resistant Staphylococcus aureus: randomised controlled trial. British Medical Journal 2015; 350: h2219

Study synopsis

This was a multi-centre, randomised, unblinded trial assessing the non-inferiority of trimethoprim/sulfamethoxazole, compared with vancomycin, for the treatment of severe infections due to methicillin-resistant Staphylococcus aureus (MRSA).

Adult patients with with severe infections caused by MRSA, including bacteraemia, and patients with highly probable MRSA infections, were eligible for inclusion. Infections were classified by standard definitions.[1] The highly probable group included patients with ventilator-associated pneumonia and prior antibiotic treatment, central catheter-related infections, and surgical site infections in the presence of a foreign body, all without positive microbiology. Patients were excluded if they had received study drugs for more than 48 hours, were diagnosed with meningitis or left sided endocarditis, or were immunocompromised.

Patients were randomised consecutively using concealed envelopes to either trimethoprim-sulfamethoxazole intravenously at a dose of 320 mg trimethoprim/1600 mg sulfamethoxazole twice daily, or vancomycin, with a starting dose of 1 g twice daily and targeting a trough between 10 and 20 mg/dL. Treatment was continued for a minimum of seven days and doses were adjusted according to renal function in both groups.

The primary efficacy outcome was clinical treatment failure at seven days and was a composite of death, persistence of fever (> 38 °C) or hypotension (< 90 mm Hg systolic or need for vasopressor support), and non-improving Sequential Organ Failure Assessment (SOFA) score. Secondary outcomes included failure or modification of treatment, bacteriological failure, defined as growth of MRSA on day 7 cultures; persistence of bacteraemia at 48 hours; length of hospital admission; and development of resistance.

To establish non-inferiority, defined as up to 15% difference in the primary outcome and assuming a 30% treatment failure rate, a sample size of 128 patients per arm was required allowing for a 10% patient drop out (α=0.05, β=0.8).

A total of 782 patients with MRSA isolates were screened, of whom 252 were included. The main reasons for exclusion were prior treatment with study drug or consent issues. 245 (97%) patients had documented MRSA infection; 91 (36%) with bacteraemia and 154

(61%) with MRSA isolated from sites. Baseline characteristics, including infection sites, were mostly balanced between groups; although the vancomycin group had more bacteraemias (P = 0.042). The median duration of treatment was 17 (95% CI, 12 to 22) days with trimethoprim-sulfamethoxazole and 14 (95% CI, 13 to 15) days with vancomycin. Other antibiotics with potential anti MRSA activity were added in 10% of the trimethoprim-sulfamethoxazole group versus 7% in the vancomycin group (P=0.32).

Overall, there was no significant difference in treatment failure at day 7 between trimethoprim-sulfamethoxazole and vancomycin (RR 1.38, 95% CI 0.96 to 1.99). However, the failure rate with trimethoprim- sulfamethoxazole was 51/135 (38%) compared with 32/117 (27%) with vancomycin, and the 95% confidence interval for the difference fell outside the lower limit of the 15% predefined for non-inferiority (–1.2% to 21.5%), indicating failure of non inferiority. Of the components comprising the composite outcome, vancomycin had lower bacteraemia persistence at day 7 and better improvement in SOFA score at day 7. There were no statistical differences in 30-day mortality or any other secondary outcomes. On multivariate analysis, allocation to trimethoprim-sulfamethoxazole was significantly associated with treatment failure (adjusted odds ratio 2.00, 1.09 to 3.65). Other independent risk factors were bacteraemia and mechanical ventilation at infection onset.

Critique

MRSA is a major public health problem and a serious therapeutic challenge. Vancomycin remains the primary agent for the empiric treatment of systemic MRSA infections as outlined in current treatment guidelines.[2] However, the emergence of less-susceptible strains[3], poor clinical outcomes[4], and increased nephrotoxicity with high-dose therapy[5] makes the search for less toxic alternatives with better or equal efficacy and easier clinical dosing a priority. Newer agents have become available, but are not without problems, being associated with dose-limiting adverse events, emerging resistance issues, and high drug costs.[3] Trimethoprim-sulfamethoxazole is an old antibiotic active against Staphylococcus aureus and has been suggested as an alternative,[6,7]. It has been recommended for the treatment of uncomplicated skin and soft tissue infections, but not for MRSA bacteraemia or pneumonia.[2] Trimethoprim-sulfamethoxazole has been previously compared in observational studies to vancomycin in the treatment of MRSA bacteraemia with similarly favourable outcomes in less severely ill patients.[8,9] With antibiotic resistance an increasing global issue, investigation of useful alternative agents already available is as potentially important as finding new ones. Therefore this trial was a good opportunity to investigate the expanded use of trimethoprim-sulfamethoxazole.

This trial was performed as a non inferiority trial. In such a study, the intent is to demonstrate an experimental treatment is not substantially worse than a control treatment, These trials are often performed where it is unethical to use a placebo. However, testing for noninferiority makes trial design and interpretation of results less

straightforward than typical superiority trials.[10-12] There are several factors which require careful consideration. Noninferiority trials aim to show an experimental treatment is not less effective than an active control by a non inferiority margin. This margin should be prospectively defined. The inferiority margin should be based on statistical and clinical judgement, and in a placebo-controlled trial, cannot be greater than the smallest response that could be reliably expected from the active treatment; or a drug with no effect could be judged simply non inferior. The margin in this trial was 15%. The investigators do not offer a justification for this, although the actual treatment response rate in the vancomycin group was 73% (the investigators estimated a pre trial 70% response) and therefore much larger than the inferiority margin. Sample size is important in all trials and there is no difference in inferiority trials except that the expectation of the new treatment effect is important, if the new treatment is thought to be more effective then a smaller population is required to show non inferiority and vice versa. The inferiority margin also affects the sample size as larger margins allow a smaller trial to be performed. Finally, the data analysis can be viewed differently. Intention-to-treat is conventionally accepted as an unbiased analytical approach, however, this may not the case for noninferiority trials, since including dropouts in the analysis tends to bias the results toward equivalence. This trial correctly reported both types of analysis.

With these considerations in mind, this trial was a reasonably large trial powered to detect a statistically relevant difference in treatment outcomes. There was an appropriate statistical plan and an interim safety analysis. The randomisation produced two similarly balanced groups in terms of size and baseline variables. Another strength was all patients received the assigned treatment drug. Finally, there was a relatively low rate of additional MRSA treatment in either group, although this is a confounding factor in the trial.

There are also some weaknesses within the trial. The trial used a composite end point; these are often used to obtain more outcome events and thus increase statistical power and their use has been debated.[13] However, it may be considered reasonable if all components of the composite are causally relevant, and in this trial they were related to treatment failure and, as such, were causally and clinically relevant. The inclusion of patients with polymicrobial infections, however, could have affected these outcomes measures. The inclusion criteria also needs to be discussed. Although the inclusion criteria allowed the recruitment of patients with symptomatic bacteraemias (91/240 patients), the majority of infections were soft tissue (88/240) or bone (71/240). Soft tissue infection patients had to meet criteria for SIRS, however, the majority of the patient population recruited were not critically ill. Only 27 patients were ventilated, only 32 had central lines (suggesting low inotrope requirements) and over half the patients had a SOFA score of zero. The investigators acknowledge this and performed a parallel observational trial[14] of the patients who were not recruited during the study period.

This population were sicker with much higher mortality, 29.1% versus 12.7% in the randomized trial; P < 0.001. Therefore, the results are not immediately transferable to the critically ill, however, the results suggest trimethoprim-sulfamethoxazole was inferior in terms of infection resolution in a less sick population, so use in sick patients seems illogical. Finally, the dosing of vancomycin and trough levels achieved (≥ 15 µg/mL in only 67% of patients) were lower than currently recommended[15], potentially resulting in an underestimation of the efficacy of vancomycin. Similarly, the dose of trimethoprim-sulfamethoxazole could have been higher.

Where it sits in the body of evidence

- In a retrospective matched cohort study, 38 patients with MRSA bacteraemia treated with co-trimoxazole, were matched with 76 patients treated with vancomycin.[8] Thirty day mortality was not significantly different between the groups (co-trimoxazole 13/38 [34.2%]; vancomycin 31/76 [40.8%]; OR 0.76, 95% CI, 0.34 to 1.7). The incidence of relapse or persistent bacteraemia was lower in the co-trimoxazole group (3/38, 7.9%) than in the vancomycin group (13/76, 17.1%), although the difference was not statistically significant (P = 0.182). Complications were similar.

- A previous randomised controlled trial recruited 101 intravenous drug abusers with Staphylococcus aureus infection (43 received trimethoprim-sulfamethoxazole and 58 received vancomycin).[16] MRSA accounted for 47% of S. aureus isolates, and 65% of patients were bacteraemic. Infections were cured in 57 of 58 vancomycin recipients and in 37 of 43 trimethoprim-sulfamethoxazole recipients (P < 0.02). Failure occurred mostly in patients with tricuspid valve endocarditis and only in those with infections caused by methicillin-sensitive Staphylococcus aureus.

- In a similar randomized, open-label, single-centre, non-inferiority trial trimethoprim/sulfamethoxazole (160 mg/800 mg three times daily) plus rifampicin (600 mg once a day) were compared to linezolid (600 mg twice a day) alone in adult patients with various types of MRSA infection.[17] One hundre4d and fifty patients were randomized; of these 56/75 (74.7%) in the linezolid group and 59/75 (78.7%) in the trimethoprim/sulfamethoxazole and rifampicin group experienced clinical success (risk difference 4%, 95% CI, -9.7% to 17.6%).

- Fifty patients with chronic osteomyelitis after debridement were randomized to cloxacillin (22 patients) for 6 weeks intravenously plus 2 weeks orally, or to rifampicin-cotrimoxazole oral therapy (28 patients) for 8 weeks.[18] During a 10 year follow-up, five relapses occurred; two (10%) in the cloxacillin and three (11%) in the rifampicin-cotrimoxazole group.

- In a small study of 34 subjects with soft tissue infections, 14 received trimethoprim-sulfamethoxazole (8 with MRSA) and 20 received doxycycline (15 with MRSA). [19] Three

of the 33 subjects (9%) with data at 14 days were classified as clinical failures. All 3 clinical failures occurred in the trimethoprim-sulfamethoxazole group (3 failures out of 14 [21%] subjects on trimethoprim-sulfamethoxazole therapy), with no clinical failures in the doxycycline group (P = 0.283).

Should we implement this into our practice?

No. Although trimethoprim-sulfamethoxazole has proven useful in dermal MRSA infections, it should not be used in place of vancomycin for severe Staphylococcal infections. Other antistaphylococcal drugs need to be tested in similar head-to-head comparisons.

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The PERMIT Trial

Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G, et al. Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. New England Journal of Medicine. 2015 June 18;372(25):2398–2408.

Study synopsis

This multi-centre, randomised, unblinded trial carried out in Canada and Saudi Arabia, assessed the effect on mortality of a restricted caloric feeding regime versus a standard regime, with preservation of protein intake in both groups.

Patients who were enterally fed within 48 hours of ICU admission were eligible for recruitment. Patients were randomised to either a restricted feeding regime of 40 to 60% of caloric requirements or a standard feeding regime of 70 to 100% of caloric requirements for 14 days, duration of ICU admission or until oral intake was established . Caloric requirements were calculated using previously published equations.[1] To ensure the permissive underfeeding group received similar amounts of enteral protein and volume to those in the standard-feeding group, the permissive-underfeeding group received additional protein (Beneprotein, Nestle Nutrition) and normal saline or water under the direction of the clinical team. The study recommended target blood glucose levels of 4.4 to 10 mmol/L. All other interventions, including selection of enteral feed, were at the discretion of the clinical team.

Assuming an estimated 90-day mortality of 25%, a total sample size of 892 patients was calculated to give an 80% power to detect an absolute difference in mortality of 8%. The primary outcome was 90-day mortality.

A total of 894 patients were randomised. Baseline characteristics were similar in the two groups; 96.8% of the patients were mechanically ventilated. During the intervention period, the permissive-underfeeding group received fewer mean (± SD) calories than the standard-feeding group (835 ± 297 kcal per day vs. 1,299 ± 467 kcal per day, $P < 0.001$; 46 ± 14% vs. 71 ± 22% of caloric requirements, $P < 0.001$). Protein intake was similar in the two groups (57 ± 24 g per day and 59 ± 25 g per day, respectively; $P=0.29$).

There was no difference in the 90-day mortality; 27.2% in the permissive-underfeeding group and 28.9% in the standard-feeding group (relative risk with permissive-underfeeding, 0.94; 95% CI 0.76 to 1.16; $P = 0.58$). There were no significant between-group differences with respect to feeding intolerance, diarrhoea, infections acquired in ICU, or ICU or hospital length of stay. The permissive-underfeeding group had lower insulin requirements, lower blood glucose concentrations and lower daily fluid balances. Post hoc analysis showed renal-replacement therapy was required less frequently in the permissive-underfeeding group 7.1% vs.11.4%; RR, 0.63; 95% CI, 0.40 to 0.98; $P = 0.04$)

Critique

Nutritional support in the acutely ill is a complex subject; this was a large pragmatic trial into one important aspect of feeding, namely caloric requirements. The rationale for adequately matching caloric intake with energy expenditure lies in the observation of accelerated muscle catabolism with caloric restriction,[2] and on the association between caloric debt and poor outcome.[3-5] Conversely, other prospective interventional trials have shown increased morbidity with higher caloric intake[6,7] and authors have speculated insufficient autophagy, a process promoted during illness leading to the removal of damaged tissue, may lead to worse outcomes.

This trial has several strengths. It was a large multi-centre randomised study, although almost 70% of patients were recruited from one centre in Saudi Arabia. The patient baseline characteristics were relatively evenly matched, in particular in terms of severity of illness, diabetes and the need for mechanical ventilation and inotropes. The under feeding group did have more severe sepsis patients. The intervention produced a good separation between the two groups in terms of calories delivered and the protocol included calories administered from non enteral feeding sources. Another protocol strength was the augmentation of protein to the under feeding group; protein metabolism is critical illness is complex. Critical illness is associated with increased proetolysis,[8] however, protein requirements during critical illness are not known, and previous studies augmenting protein intake have produced conflicting results.[9,10] The trial design ensured both groups received equal amounts of protein, and therefore avoided a confounding variable associated with reduced enteral intake. Efforts to ensure equal volumes were also included, but were less successful, with the underfeeding group receiving less volume. Finally, the data collection and patient follow up during this trial was impressive, with only 9 patients not included in the final results.

There also some weaknesses within the trial. By the authors own admission, the study was powered to detect an 8% absolute risk reduction. The study may therefore have failed to show a true, but small treatment effect. The protocol excluded 86% of screened patients, the majority of whom did not meet inclusion criteria as they were either orally feed or not commenced on enteral nutrition. Within the randomised population, there was a relatively low percentage of surgical patients (3.5%) and it is unclear if these patients were either not commenced on enteral nutrition or treated with parenteral nutrition and therefore excluded. The trial, therefore, had mainly medical patients and potentially limiting it's generalisibility. The trial used equations to calculated energy and enteral nutrition requirements; however, these are prone to error.[11] Assessment of energy requirements in critical illness is a major challenge. Guidelines from both the European Society for Clinical Nutrition and Metabolism and the American Society for Parenteral and Enteral Nutrition recommend the use of indirect calorimetry.[12,13] The trial was not blinded for the delivery of the intervention and it is difficult to assess if this influenced outcomes. Of note, the intake volume of the

underfeeding group was lower compared to the full feed group.

The investigators concluded moderate caloric feeding with maintenance of full protein requirement, compared to standard full feeding, was not associated with reduced mortality. However, the target caloric intake was not reached in some patients. In particular, the standard feed group only received on average 70% of caloric targets. The trial could perhaps therefore be described as a comparison of permissive underfeeding versus less severe permissive underfeeding.

Finally, the only notable positive outcome was the reduced incidence of renal replacement therapy in the underfeeding group. This was a a post-hoc analysis and should be interpreted cautiously.

Where it sits in the body of evidence

- One hundred and twenty patients undergoing gastrectomy in five hospitals were randomly assigned to receiving parenteral nutrition at 30 kcal/ kg/day and 0.2 g/kg/day of nitrogen, or hypocaloric nutrition, consisting of 18 kcal/kg/day and 0.10g/kg/day of nitrogen.[14] There were less infectious complications for the hypocaloric group, at 3.3% versus 16.6%; P = 0.0149). The SIRS rate was also significantly lower (25% vs 45.0%; P = 0.0216), and the postoperative duration of hospital stay was shorter at 12.4 days ± 4.0 versus 14.1 days ± 5.8 days (P=0.047) for the hypocaloric group.

- In a prospective, controlled, clinical trial performed in a medical ICU, 150 patients were randomised to an early-feeding group or late-feeding group.[15] During five days of mechanical ventilation, the total intake of calories (2,370 ± 2,000 kcal versus 629 ± 575 kcal; P < 0.001) and protein (93.6 ± 77.2 g versus 26.7 ± 26.6 g; P < 0.001) were statistically greater for the early-feeding group. Patients in this group had statistically greater incidences of ventilator-associated pneumonia (49.3% versus 30.7%; P = 0.020) and Clostridium difficile infection (13.3% versus 4.0%; P = 0.042). The early-feeding group also had longer ICU (13.6 ± 14.2 days versus 9.8 ± 7.4 days; P = 0.043) and hospital lengths of stay (22.9 ± 19.7 days versus 16.7 ± 12.5 days; P = 0.023). There was no between-group difference in hospital mortality (20.0% versus 26.7%; p = 0.334).

- In a single-centre trial, 130 mechanically ventilated patients receiving enteral nutrition (EN), were randomized to an energy target determined by repeated indirect calorimetry measurements (study group, n = 56), or a set nutritional intake of 25 kcal/kg/day (control group, n = 56).[7] Patients in the study group had a higher mean energy (2,086 ± 460 vs. 1,480 ± 356 kcal/day, P = 0.01) and protein intake (76 ± 16 vs. 53 ± 16 g/day, P = 0.01). There was a trend towards an improved hospital mortality in the study group (32.3% vs. 47.7%, P = 0.058), whereas length of ventilation (16.1 ± 14.7 vs. 10.5 ± 8.3 days, P = 0.03) and ICU stay (17.2 ± 14.6 vs. 11.7 ± 8.4, p = 0.04) were increased.

- In a randomised 2 x 2 factorial trial, 240 adult critical care patients were randomised to permissive underfeeding or target feeding groups (caloric goal, 60-70% compared with 90-100% of calculated requirement, respectively) with either tight or liberal blood sugar control (4.5 – 6.0 mmol/L vs 10.0 – 11.1 mmol/L). Twenty-eight day mortality was 18.3% in the permissive underfeeding group compared with 23.3% in the target feeding group (RR, 0.79; 95% CI, 0.48 to 1.29; P = 0.34). However, hospital mortality was lower in the permissive underfeeding group (30.0% compared with 42.5%; RR, 0.71; 95% CI, 0.50 to 0.99; P = 0.04). No significant differences in outcomes were observed in the blood glucose groups.

- In this large multi-center trial, 4,640 ICU patients were randomised to early (< 48 hrs) or late (> 8 days) supplementation of enteral by parenteral nutrition, resulting in a hypocaloric group and a fully fed group. [6] Patients in the late-initiation group had a relative increase of 6.3% in the likelihood of being discharged alive earlier from the ICU (HR, 1.06; 95% CI, 1.00 to 1.13; P = 0.04) and from the hospital (HR, 1.06; 95% CI, 1.00 to 1.13; P = 0.04). Rates of death in ICU and in-hospital, as well as rates of survival at 90 days were similar between the two groups. 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) a lower incidence of cholestasis (P < 0.001), a lower rate of prolonged (> 48 hrs) ventilation (P = 0.006) and a median reduction of 3 days in the duration of renal-replacement therapy (P = 0.008).

- In a further trial, 83 critically ill patients were randomly allocated to receive standard daily caloric requirement of 25-30 kcal/kg/day (eucaloric) or 50% (hypocaloric) via enteral or parenteral nutrition, with an equal protein intake (1.5 g/kg/day).[17] Glucose control was similar. There were no differences in the mean number of infections between the hypocaloric group and eucaloric group (2.0 ± 0.6 and 1.6 ± 0.2, respectively; P = 0.50) Mean ICU length of stay (16.7 ± 2.7 and 13.5 ± 1.1 d; P = 0.28) and hospital length of stay (35.2 ± 4.9 and 31.0 ± 2.5 d; P = 0.45) were similar. Mortality was not affected [3 (7.3%) and 4 (9.5%), respectively; P = 0.72].

- In an open-label study, 200 patients with acute respiratory failure were randomised to receive either initial trophic (10 mL/hr) or full-energy enteral nutrition for the initial 6 days of ventilation.[18] The trophic group received an average of 15.8% ± 11% of goal calories daily compared to 74.8% ± 38.5% (P < 0.001). Both groups had a median of 23.0 ventilator-free days (P = 0.90) and a median of 21.0 intensive-care-unit-free days (P = 0.64). Mortality was similar (22.4% trophic group vs. 19.6% full-energy group; P = 0.62). The trophic group had fewer episodes of elevated gastric residual volumes (2% vs. 8% of feeding days; P < 0.001).

- In the open label, multi-centre EDEN study, 1,000 adults patients with ARDS were randomized to receive either trophic or full enteral feeding for the first 6 days before

reverting to full feeding.[19] The full-feeding group (492 patients) received more enteral calories for the first 6 days, approximately 1,300 kcal/d compared with 400 kcal/d (P < 0.001). Initial trophic feeding did not increase the number of ventilator-free days (14.9 [95% CI, 13.9 to 15.8] vs 15.0 [95% CI, 14.1 to 15.9]; P = 0.89) or reduce 60-day mortality (23.2% [95% CI, 19.6% to 26.9%] vs 22.2% [95% CI, 18.5% to 25.8%]; compared with full feeding. There were no differences in infectious complications between the groups. The full-feeding group experienced more gastrointestinal upset, had higher plasma glucose values and required more average hourly insulin. At one year follow up there were no differences in outcome measures[20].

Should we implement this into our practice?

Possibly. The PermiT trial adds to the body of evidence challenging the concept of benefit with early full feeding in critical illness. Consequently, early invasive or costly interventions aiming at quickly achieving up-to-target intake of energy or protein are probably not required.

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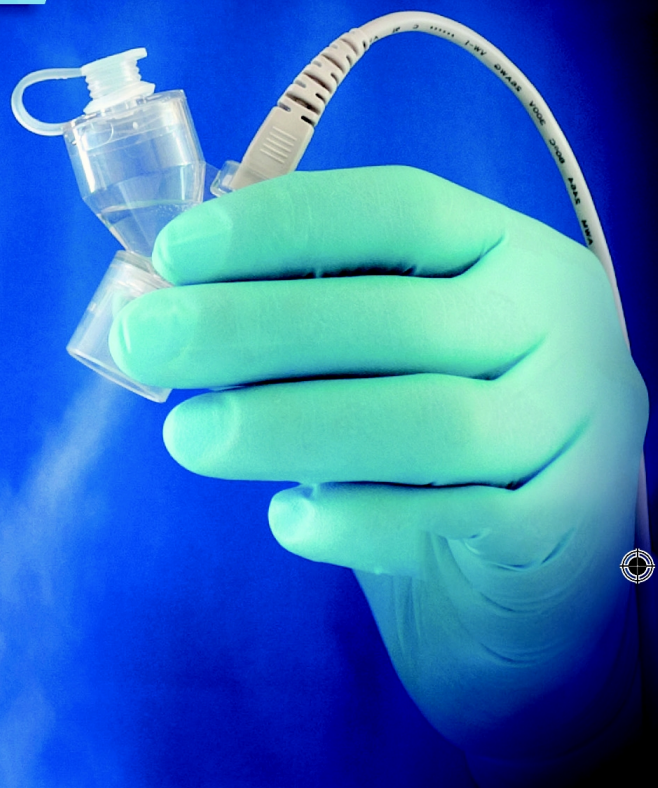

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Study synopsis

This was a single centre, randomized, open label trial performed in an intensive care unit in China. Its primary aim was to investigate the effects of esmolol and milrinone on heart rate control in patients with septic shock.

Patients who were admitted to the adult ICU with suspected infection, met SIRS criteria and had a heart rate above 95 beats/min after resuscitation were eligible for recruitment. Exclusions were asthma, bradycardia, heart block or allergy to study drug. Randomisation was performed by a computer in a ratio of 1:1:1 to three different groups: control (C) group, milrinone (M) group, and milrinone–esmolol (ME) group.

After fluid resuscitation, noradrenaline was commenced to maintain a mean arterial blood pressure above 65 mmHg. Subsequently, patients in the M group were additionally treated with a continuous intravenous infusion of milrinone, commenced with a loading dosage of 30 ug/kg and maintained between 0.375–0.5 ug/kg/min. Patients in the ME group received both milrinone and esmolol with dose tritrated to maintain the heart rate between 75 and 94 beats/min. The intervention was continued for 96 hours. All patients had cardiac ouptut monitoring using the PICCO device. Haemodynamic parameters including MAP, central venous pressure (CVP), heart rate, cardiac index (CI) and stroke volume index (SVI); and noradrenaline dosages were recorded. Blood samples were collected at baseline and 24, 48, 72, and 96 hours for TNF-a and IL-6, as well as markers of myocardial injury, including CK-MB, troponin I, and brain natriuretic peptide.

The primary outcome was the reduction of heart rate to lower than the predefined threshold of 95 beats/min and maintenance within the target range between 75 and 94 beats/min during the first 96 hrs. Secondary outcomes included 28-day survival, ICU and hospital length of stay, noradrenaline requirements, changes in hemodynamic variables, organ dysfunction, myocardial injury markers, pro-inflammatory factors in the serum, and adverse drug events.

The sample size of 30 patients per group was calculated to provide 80% power with a two-sided 5% significance level to detect a 20 beats/min reduction in heart rate, assuming a standard deviation (SD) of 25 beats/min and a 10% drop out rate.

Ninety patients were enrolled into the three treatment groups. Baseline variables were

similar. In particular, there were similar sources of infection and positive blood cultures, severity of illness scores and baseline heart rates.

The rates of successful heart rate control at 96 hours were 43.3%, 53.3%, and 100 %, respectively, for the C, M and ME groups. There was a significant statistical difference between the ME and M groups ($P < 0.001$), as well as between the M and C groups ($P < 0.001$). Before treatment, the haemodynamics were comparable in each group. After 12 hours, and for the rest of the intervention, there was no significant difference in MAP or CVP. However, the heart rates of patients in the ME group were significantly lower than those patients in the C and M groups ($P < 0.05$). The cardiac indexes and stroke volume indexes in both milrinone groups were significantly higher than in the control group after 12 hrs treatment ($P < 0.05$) and this persisted until the end of the intervention. There were no differences in noradrenaline requirements until 72 hrs, when both the milrinone groups required significantly less vasopressor ($P < 0.05$). There was less renal and liver dysfunction in the milrinone groups after 96 hrs treatment ($P < 0.05$). In addition, the esmolol group has significantly reduced markers of cardiac damage ($P < 0.05$) and inflammation. Duration of stay was similar in all groups although survival was higher in the ME group than in the M (Log rank statistic = 5.452; $P = 0.020$) and C (Log rank statistic = 10.206; $P = 0.001$) groups.

Critique

Beta blockers reduce myocardial oxygen consumption and this has produced interest in the role of beta blockers both peri-operatively and in critical illness. While routine peri-operative beta blockade cannot currently be recommended,[1] the role of beta blockers in critical illness remains to be defined. Specifically in sepsis, adrenergic stimulation results in cardiac stimulation (increased contractility, heart rate and myocardial oxygen demand) as well as a host of other metabolic and immune effects.[2] The increased cardiac contractility and heart rate may initially meet the increased systemic metabolic demand, however, up to 60% of patients subsequently develop reduced ejection fraction with apical ballooning and myocardial stunning.[3] The aetiology of septic cardiomyopathy remains unclear but excess adrenergic activation is one possible cause, explaining the potential protective role of beta blockade.[4] The modulation of extra cardiac effects may also be important.

Alternatively, beta blockers may have beneficial effects simply in terms of heart rate control, better diastolic filling and reduction in myocardial oxygen demand.[5] Equally, the concept of commencing a drug which could potentiate hypotension and organ perfusion requires careful consideration. However, previous observational data has associated the use of preadmission beta blockade with increased survival in sepsis.[6] The physiological concept of improved myocardial function has been shown in a rat model of sepsis[7] and the use of beta blockade in septic critically unwell patients was previously proven to be possible.[8] There has been one previous randomized trial using esmolol in sepsis with a

positive effect on mortality demonstrated.[9] The results have been questioned, however, due to an excessive mortality in the control arm. On the current level of evidence, the investigation of careful beta blockade in sepsis can be justified.

This was an interesting small randomised trial. The investigators postulated by inhibiting the activation of sympathetic nerves by beta-blockade, the potentially damaging effects of catecholamines might be reduced. Consequently, when combined with milrinone, a phosphodiesterase III inhibitor which has been shown to improve heart contractility in patients with septic shock,[10] overall haemodynamics and outcome might be improved. It used the internationally recognised SIRS criteria, with the additional criteria that patients had a relevantly elevated heart rate after resuscitation. A power calculation was provided, although without an explanation why the chosen 20 beats/min reduction in heart rate is clinically relevant. There was an appropriate randomization process, producing groups that were relatively well matched in terms of demographics and haemodynamics at baseline. These patients were also sick, with mean APACHE II scores ranging from 20.6 ± 5.8 to 21.2 ± 5.7, bacteraemias in 43/90 patients and mean noradrenaline requirement between 0.23 - 0.28 mcg/kg/min. However, the median ages ranged from only 33 to 38, signifing a young study group which may not be reflective of the general ICU population. Data collection was comprehensive, with the trial completing without withdrawals.

There are some limitations in this trial. This was a non blinded trial and therefore prone to bias, although due to the physiological effects of beta blockers, blinding would have been difficult. The study was based and powered on the primary outcome of a reduction in heart rate, as happened in a previous trial,[9] however, this was an arbitary target. It is difficult to relate this to a clinically relevant end point. The dose of esmolol was neither standardised nor titrated to more meaningful effects such as attempting to optimise diastolic filling, but simply to this general pre determined goal of a heart rate between 75 and 94 beats/min. Perhaps, the use of more individualised targets using echocardiography might have made the heart rate target more meaningful. Furthermore, there is a lack of detail provided in the protocol and presented results. The pre trial resuscitation was by goal directed therapy but we are not provided with any details of fluid resuscitation administered for instance. Perhaps this is less important as the baseline haemodynamic variable were similar.

The investigators do not provide any details on how milrinone was titrated and to what goals. Milrinone has multiple haemodynamic effects including on the primary outcome of heart rate control but also cardiac index.[11] The extent to which milrinone offsets the negative inotropic effects of esmolol and thus minimises the potential detrimental impact of β-blockade on haemodynamics, cannot be determined from this study. Other potential confounding variables such as the use of other inotropes or steroids are not rported, and we have no details on the use of fluids during the study period. All of these

could have major impact on both the primary and secondary outcomes.

Another limitation is the trial failed to incorporate echocardiography measurements, which would have potentially added to the usefulness of the data collected in terms of effects of the interventions on cardiac volumes and ejection fractions; although a cardiac output monitor was used. Finally, the trial reported on mortality, for which it was not powered, however, and again as with a previous similar trial[9], the mortality in the control group was higher than expected at 60%. This excess mortality may have been because of the small size of the trial, where a small number of deaths could have a significant impact. However, the control group had sustained elevated lactates, even after 96 hours of treatment, which questions the standard treatment received by this group.

The investigators conclude the combination therapy with milrinone and esmolol could improve cardiac function and 28-day survival rates in patients with severe sepsis. However, this was a small trial which has only perhaps shown that a beta blocker can be incorporated into a protocol for the treatment of sepsis. Further work is required in terms of goals for beta blocker titration, interaction with other vasoactive agents, myocardial performance parameters, and investigation of the extra cardiac effects before perhaps larger trials on relevant, important clinical outcome can be conducted.

Where it sits in the body of evidence

- In a small study muscle protein kinetics were quantified using isotopic tracer in six septic, mechanically ventilated patients with pneumonia before and after a 3-hour infusion of esmolol, targeted to reduce heart rate by 20% from baseline. Haemodynamic measurements were performed using a thermodilution pulmonary artery catheter. Selective beta adrenergic blockade was associated with a 20% reduction in heart rate and a comparable decrease in cardiac output. Esmolol administration failed to affect systemic or pulmonary vascular resistance, oxygen consumption, hepatic or leg blood flow, energy expenditure, or ATP availability/energy change within muscle.[12]

- In a retrospective analysis, the combined use of milrinone and enteral metoprolol therapy was used in 40 patients with septic shock. In all patients, beta blockers were initiated only after stabilization with a target heart rate < 95 beats per minute. Heart rate control (65 to 95 bpm) was achieved in 97.5% of patients (n = 39). Heart rate, central venous pressure, and noradrenaline, arginine vasopressin, and milrinone dosages decreased (all $P < 0.001$). Cardiac index and cardiac power index remained unchanged whereas stroke volume index increased ($P = 0.002$). pH increased ($P < 0.001$), whereas arterial lactate ($P < 0.001$), serum C-reactive protein ($P = 0.001$), and creatinine ($P = 0.02$) levels decreased during the observation period. Twenty-eight-day mortality was 33%.[13]

- After correction of preload, an esmolol bolus (0.2 - 0.5 mg/kg), followed by continuous 24 hr infusion, was administered in ten septic patients.[14] Monitoring with echocardiography and pulmonary artery catheter was performed. Heart rate decreased from mean 142 ± 11/min to 112 ± 9/min ($p < 0.001$), with parallel insignificant reduction of cardiac index (4.94 ± 0.76 to 4.35 ± 0.72 L/min/m^2). Stroke volume insignificantly increased from 67.1 ± 16.3 ml to 72.9 ± 15.3 ml. No parallel change of pulmonary artery wedge pressure was observed (15.9 ± 3.2 to 15.0 ± 2.4 mmHg), as well as no significant changes of noradrenaline infusion (0.13 ± 0.17 to 0.17 ± 0.19 mg/kg/min), DO_2, VO_2, OER or arterial lactate.

- In an retrospective observational study of 9,465 patients hospitalized in critical care units for sepsis, 1,061 patients were on chronic prescription with β-blockers and 8,404 were not previously treated.[6] Despite a higher risk profile, patients previously prescribed with β-blockers had lower mortality at 28 days (188/1061 [17.7%]) than those previously untreated (1,857/8,404 [22.1%]) (OR 0.78; 95% CI 0.66 to 0.93; P = 0.005 for unadjusted analysis, and OR 0.81; 95% CI 0.68 to 0.97; P = 0.025 for adjusted analyses). Sensitivity and pair-matched results confirm the primary findings.

- In a small prospective, observational clinical study, after 24 hrs of haemodynamic optimization, 25 septic shock patients with a heart rate above 95 beats per minute and requiring noradrenaline were given a titrated esmolol infusion to maintain heart rate less than 95 beats per minute.[15] Heart rates targeted between 80 and 94 beats per minute were achieved in all patients. Whereas cardiac index decreased (4.0 [3.5; 5.3] vs 3.1 [2.6; 3.9] L/min/m; P < 0.001), stroke volume remained unchanged (34 [37; 47] vs 40 [31; 46] mL/beat/m; P = 0.32). Microcirculatory blood flow in small vessels increased (2.8 [2.6; 3.0] vs 3.0 [3.0; 3.0]; p=0.002). PaO_2 and pH increased while $PaCO_2$ decreased (all P < 0.05). Of note, noradrenaline requirements were significantly reduced by selective β-1 blocker therapy (0.53 [0.29 to 0.96] vs 0.41[0.22 to 0.79] µg/kg/min; p=0.03).

- In the largest randomized study, involving 154 patients in septic shock with a heart rate of 95/min or higher requiring high-dose noradrenaline, 77 patients were randomised to receive an infusion of esmolol titrated to maintain heart rate between 80/min and 94/min for their ICU stay and 77 patients to standard treatment. [9] Targeted heart rates were achieved in all patients in the esmolol group, compared with those in the control group, with a mean reduction of 18/min (P < 0.001). The stroke volume index (P = 0 .02) and noradrenaline (P = 0.003) requirements were significantly reduced in the esmolol group. Fluid requirements were also reduced (P < 0.001). Twenty-eight day mortality was 49.4% in the esmolol group vs 80.5% in the control group (adjusted hazard ratio, 0.39; 95% CI, 0.26 to 0.59; P < .001). There was a high incidence of levosimendan use in this study.

Should we implement this into our practice?

No. This is an interesting and exciting early clinical trial demonstrating beta1-adrenergic blockade to a targeted heart rate can be administered safely in vasopressor-dependent tachycardic septic patients. Further evidence is required before a change in practice is justified.

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The CLOSE Trial

Panwar R, Hardie M, Bellomo R, Barrot L, Eastwood GM, Young PJ, et al. Conservative versus liberal oxygenation targets for mechanically ventilated patients – a pilot multicenter randomized controlled. Am J Respir Crit Care Med 2016;193(1):43-51

Study synopsis

This multi-centre, parallel group, randomised trial was performed in four intensive care units in Australia, New Zealand and France. The primary aim of this pilot study was to test the hypothesis that conservative oxygen therapy is feasible and safe.

Adult patients admitted to the ICU who were ventilated for < 24 hours and their treating clinician expected ventilation to continue for at least next 24 hours were eligible for enrolment. Exclusions were pregnancy, those not expected to survive, or if the treating clinician lacked equipoise for the patient to be enrolled in this trial. Randomisation was done in a masked fashion, using opaque sealed envelopes, with a unique computer-generated, permuted block randomization.

Following randomisation, patients were assigned SpO_2 targets of 88 - 92% for the conservative oxygenation group or ≥ 96% SpO_2 for the liberal oxygenation group. The bedside nurse titrated the FiO_2 within a range of 0.21 to 0.80 to achieve the SpO_2 target, whilst PEEP levels were determined by the treating clinicians. The study intervention was continued whilst the patient remained ventilated. The treating ICU physician could alter oxygenation targets at any time. Data on oxygenation parameters and ventilator settings were recorded 4-hourly from day 0 to day 7.

The primary outcome was the mean area-under-curve (AUC) for SpO_2, SaO_2, PaO_2 and FiO_2 on days 0 - 7. Secondary safety endpoints were change from baseline SOFA score, changes in PaO_2/FiO_2, new-onset ARDS, changes in creatinine, incidence of haemodynamic instability, defined as cardiac arrest or addition of ≥ 2 new vasopressor/inotrope agents), vasopressor-free days, arrhythmia-free days, and ventilator-free days until day 28, ICU and 90-day mortality.

The sample size calculation was based on observational data to estimate sufficient patient exposure to mechanical ventilation. An estimated 100 patients were required to have 350 days of mechanical ventilation.

The trial enrolled 104 mainly medical patients. Fifty-three patients were randomized to the conservative oxygenation group and 51patients to the liberal oxygenation group. After one withdrawal, 103 patients were analysed. Baseline characteristics were similar. There was no difference in ventilator strategies, fluid administration or blood

transfusion over the trial period, although the conservative group had more blood gases performed. In terms of the primary outcome, participants spent the majority of time within the intended target range in both groups. The mean AUC and 95% CI for SpO_2, SaO_2, PaO_2 and FiO_2 were significantly lower in the conservative group compared to the liberal group. Overall, participants spent a median of 6% [IQR 0 - 25%] time off target, but more time was spent off target in the conservative arm than in the liberal arm (14% vs. 3%, p <0.001). Daily mean SpO_2, PaO_2 and FiO_2 for the groups were well separated on all seven days of ventilation. Participants in the conservative group spent more time at an FiO_2 of 0.21 than those in the liberal group. There were no significant differences in any secondary outcomes measures.

Critique

Oxygen is vital for mammalian cell survival and oxygen supplementation has been a cornerstone of resuscitation to avoid the harmful effects of hypoxaemia. However, although the detrimental effects of hyperoxia thought to be mediated through free radial production on the respiratory[1] and cardiovascular[2] systems have been previously known, until recently, consideration of the potential for adverse clinical outcomes has had less attention. Some observational data exists suggesting that hyperoxia may have negative effects in traumatic brain injury,[3,4] stroke and subarachniod haemorrhage[5] and cardiac arrest,[6,7] conditions where ischaemia and reperfusion are particularly important. However, the evidence is far from conclusive.[8,9] In the ICU, the ideal arterial oxygen partial pressure target is unknown. A large observational study suggested a U-shaped relationship with increased mortality above thirty and below nine kPa.[10] However a larger observational study confirmed the negative effects of hypoxaemia, but failed to correlate hyperoxia with outcomes.[11] In our clinical practice in some patient populations, oxygen therapy is already limited. Guidelines suggest COPD patients should have titrated oxygen[12] and in the acute respiratory distress syndrome, lower oxygen targets have become acceptable.[13,14] However, in the general intensive care population, evidence suggests that, in reality, oxygen administration is more liberal than conservative.[15,16] Therefore with conflicting observational data, differences in practice and a lack of clinical trials, this study can start to answer some important and fundamental questions on probably the commonest intervention in critical care.

This was a fascinating study in an area that requires more research.[17] The study has multiple strengths. It is the first randomised multi-centre trial investigating the feasibility of conservative versus liberal use of oxygen in an intensive care population. The study successfully randomised 103 patients to groups of similar baseline characteristics. The protocol produced a clear separation between the liberal and conservative groups and the time that patients deviated from the target saturations was low. The study adequately monitored for safety issues and showed that episodes of severe hypoxaemia were uncommon. Overall, the authors have demonstrated that such

a trial is possible.

There are also some limitations. This was a feasibility study only, and was not powered for clinical outcomes. The only strong conclusion that can be drawn is the trial process was relatively successful and a larger study is possible. The trial enrolled 103 out of 357 screened patients, with 120 patients having been ventilated for more than 24 hours. The inability to randomise these patients is probably of little significance in this feasibility study. However, 69 patients were not randomised due to a lack of equipoise. The reasons for these decisions were not recorded and the the investigators speculate these might be COPD patients where conservative oxygen strategies are already recommended. However, this may have implications for a larger clinical outcomes trial, and the reasons for these exclusion need to be clarified to ensure the results of a larger trial are representative of the general ICU population. The population in this small trial was mixed, but was predominantly medical patients. Again the reasons for the low recruitment of surgical and trauma patients would be valuable in planning a larger trial. Perioperative hyperoxia is associated with less wound infections[18] and perhaps there was an unwillingness to subject these patients to lower oxygen concentrations. Furthermore, perhaps its not unsurprising that in trauma, where patients are potentially bleeding and therefore losing oxygen carrying capacity, clinicians are reluctant to restrict oxygen delivery. A further limitation is the trial was not blinded, however, such an intervention cannot be blinded, and the trial used predefined statistics in order to minimise this effect. The implications for a larger trial is difficult to predict; perhaps an outcome assessor could at least be blinded to the intervention.

If we examine the actual intervention, the trial results did produce a good separation in patient group saturations, arterial oxygen partial pressures and oxygen delivered. However, in the conservative group the mean saturations were higher than their target, with the investigators claiming this was primarily due to the limit of FiO_2 titration, since it was not possible to titrate FiO_2 below 0.21. The question has to be asked whether these patients were actually that unwell and whether this is the right population to study, if it is likely the interventions will make more of a difference in unwell patients. The conservative group also spent more time out of the defined target area than the liberal group - essentially at higher saturations, as there was only one reported desaturation. Clinicians were allowed to increase FiO_2 as necessary, which could also have had an influence.

Finally, the authors in this study defined conservative as 88% - 92% saturations and liberal above 96% saturations. For the conservative group there is no defined levels of permissive oxygenation,[17] but the human body can tolerate extremely low PaO_2 levels,[19] but the for how long and at what level is not clear. Neonatal data perhaps suggests 88% - 92% may be a suitable choice.[20] There are similar issues with the liberal group. A meta analysis[21] found heterogeneity in criteria used for defining hyperoxia exposure.

Furthermore, it was unclear if early exposure, the highest exposure or if the overall effect depended on the total amount of excess O_2 received. Given the observational data by de Jonge[10], perhaps only the extremes of oxygenation make a difference.

The authors plan further larger trials which are required to clarify the titration of oxygen in critical illness.

Where it sits in the body of evidence

General ICU

- In a retrospective, observational study on 36,307 consecutive ventilated patients in 50 Dutch ICUs, and based on their first 24 hours in the ICU, in-hospital mortality was shown to be linearly related to FiO_2 value and had a U-shaped relationship with PaO_2, with both lower and higher PaO_2 values being associated with a higher mortality.[10]

- Another retrospective study of 152,680 patients assessed the 'worst' alveolar-arterial (A-a) gradient during the first 24 hours of ICU admission for all ventilated adult patients.[11] Multivariate analysis was used to determine the relationships between PaO_2 and mortality, and also the worst PaO_2, admission PaO_2 and peak PaO_2 in a random cohort of patients. There was an association between progressively lower PaO_2 and increasing in-hospital mortality, but not with increasing levels of hyperoxia.

- In a pilot prospective before-and-after study assessing the feasibility and safety of a conservative approach to oxygen therapy in mechanically ventilated ICU patients, a total of 105 adult were assigned to a conventional before period (n = 51) and to an after period, which consisted of a change to conservative oxygen therapy (n = 54). [22] SpO_2 during mechanical ventilation fell from 98.4% (IQR, 97.3 to 99.1) to 95.5% (IQR, 94.0 to 97.3) ($P < 0.001$). The median PaO_2 changed from 107 torr (94 to 131) to 83 torr (71 to 94), ($P < 0.001$), with a change to a median FiO_2 from 0.40 (0.35 to 0.44) to 0.27 (0.24- to 0.30) ($p < 0.001$).

Cardiac Arrest

- In a multi-center cohort study using the Project IMPACT critical care database, post cardiac arrest patients were divided into 3 groups defined on PaO_2 on the first arterial blood gas in the ICU.[6] Hyperoxia was defined as PaO_2 of 300 mmHg or greater; hypoxia, PaO_2 of less than 60 mmHg and normoxia in between. Of 6,326 patients, 1,156 had hyperoxia (18%), 3,999 had hypoxia (63%), and 1,171 had normoxia (19%). The hyperoxia group had significantly higher in-hospital mortality (OR for death, 1.8; 95% CI, 1.5 to 2.2).

- In another observation study, 12,108 post cardiac arrest patients were divided into three groups using identical criteria to the previous trial. [23] 1,285 patients (10.6%) had

hyperoxia, 8,904 (73.5%) had hypoxia/poor O_2 transfer, 1,919 (15.9%) had normoxia and 1,168 (9.7%) had isolated hypoxaemia (PaO_2 < 60 mmHg). Hyperoxia was associated with an odds ratio for hospital death of 1.2 (95% CI, 1.1 to 1.6). However, after Cox proportional hazards modelling of survival, hyperoxia had no independent association with mortality. Importantly, after adjustment for FiO_2 and the relevant covariates, PaO_2 was no longer predictive of hospital mortality (P = 0.21).

- In another multi-centre cohort study using the Project IMPACT post cardiac arrest database, the association between PaO_2 (continuous variable) and mortality was tested.[7] Of 4,459 patients, 54% died. Over ascending ranges of oxygen tension, there was significant linear trends of increasing in-hospital mortality and decreasing survival as functionally independent. There was no evidence supporting a single threshold for harm from supranormal oxygen tension.

- In a retrospective study, 170 patients treated with hypothermia after cardiac arrest were analysed.[24] Of 170 patients, 77 (45.2%) survived to hospital discharge. Survivors had a significantly lower maximum PaO_2 (198 mm Hg; IQR, 152.5 to 282) measured in the first 24 hrs following cardiac arrest compared to non-survivors (254 mm Hg; IQR, 172 to 363; P = 0.022). A multivariable analysis revealed higher levels of PaO_2 were significantly associated with increased in-hospital mortality (OR 1.439; 95% CI, 1.028 to 2.015; P = 0.034) and poor neurological status at hospital discharge (OR, 1.485; 95% CI 1.032 to 2.136; P = 0.033).

- Using the Victorian Ambulance Cardiac Arrest Registry, 584 patients were allocated into three groups (hypoxia [PaO_2 < 60 mmHg], normoxia [PaO_2, 60 to 299 mmHg] or hyperoxia [$PaO_2 \geq 300$ mmHg]) according to their most abnormal PaO_2 level in the first 24 hours of ICU stay.[25] The relationship between PaO_2 and hospital mortality was investigated. The unadjusted hospital mortality was 51% in the hypoxia patients, 41% in the normoxia patients and 47% in the hyperoxia patients (P = 0.28). After adjustment for cardiopulmonary resuscitation by a bystander, patient age and cardiac arrest duration, hyperoxia in the ICU was not associated with increased hospital mortality (OR, 1.2; 95% CI, 0.51 to 2.82; P=0.83).

- In a retrospective observational study including 213 adult cardiac arrest patients, the cohort was divided into four categories based on the distribution of the mean PaO_2.[26] The primary outcome was in-hospital mortality. In the multivariate analysis, there was a V-shaped independent association between the mean PaO_2 and poor neurological outcome at hospital discharge, with the risk of poor neurological outcome increasing with a descending and ascending PaO_2 ranges.

HEAD Injury

- In a registry-based analysis, the relationship between early hypoxaemia and hyperoxaemia on outcome from moderate-to-severe traumatic brain injury was investigated.[27] Patients were stratified by arrival PaO_2. Logistic regression was used to quantify the relationship between hypoxemia, hyperoxemia, and outcome from TBI. A total of 3,420 patients were included. TRISS calculations revealed worse outcomes than predicted for both hypoxemia and extreme hyperoxemia. Logistic regression demonstrated an optimal PaO_2 range (110 to 487 mmHg), with an independent association observed between decreased survival and both hypoxemia (OR, 0.54; 95% CI, 0.42 to 0.69; $P < 0.001$) and extreme hyperoxemia (OR, 0.50; 95% CI, 0.36 to 0.71; $P < 0.001$).

- In a retrospective cohort of 1,547 patients with traumatic brain injury, logistic regression analysis was used to determine whether average high (> 200 mm g) or low (< 100 mmHg) PaO_2 levels within the first 24 hours of hospital admission correlated with patient outcomes.[3] The mortality rate was 28%. After controlling for age, sex, Injury Severity Score, mechanism of injury, and admission GCS score, patients with high PaO_2 levels had significantly higher mortality and lower discharge GCS scores than patients with a normal PaO_2 ($P < 0.05$). Patients with low PaO_2 levels also had increased mortality ($P < 0.05$).

- The Finnish Intensive Care Consortium database was screened for mechanically ventilated patients with a moderate-to-severe TBI.[8] Patients were categorized, according to the highest measured alveolar-arterial O_2 gradient or the lowest measured PaO_2 value during the first 24 hours of ICU admission, to hypoxaemia (< 10.0 kPa), normoxaemia (10.0 to 13.3 kPa) and hyperoxaemia (> 13.3 kPa). A total of 1,116 patients were included in the study, of which 16% (n = 174) were hypoxaemic, 51% (n = 567) normoxaemic and 33% (n = 375) hyperoxaemic. The total 6-month mortality was 39% (n = 435). After multivariate analysis, there was no correlation with oxygenation and outcome.

- In this single-centre retrospective study on 193 patients with severe TBI, the effects of 50 mmHg incremental PaO_2 thresholds during the first 72 hours on discharge survival were examined.[28] Overall survival was 57%. PaO_2 thresholds in increments of 50 mmHg between 250 and 486 mmHg (68%) were associated with discharge survival in patients with severe TBI. This association between PaO_2 thresholds and survival was sustained until a PaO_2 of 486 mmHg (adjusted OR,3.4; 95% CI, 1.5 to 7.7). In-hospital hypoxaemia was common (24%) and associated with mortality (survival adjusted OR, 0.46; 95% CI 0.22 to 0.95).

- In another retrospective multi-centre cohort study, the hypothesis that hyperoxia was

not associated with higher mortality in traumatic brain injury was tested.[4] Hyperoxia was defined as PaO_2 ≥300 mm Hg (39.99 kPa), hypoxia as any PaO_2 <60 mm Hg (7.99 kPa) or PaO_2/FiO_2 ratio ≤300 and normoxia, defined as neither hyperoxia or hypoxia. The primary outcome was in-hospital mortality. 1,212 ventilated TBI patients were identified, of whom 403 (33%) were normoxic, 553 (46%) were hypoxic and 256 (21%) were hyperoxic. The mortality was highest in the hypoxic group (224/553 [41%], crude OR, 2.3; 95% CI, 1.7 to 3.0, P < 0.0001), followed by hyperoxic (80/256 [32%], crude OR, 1.5; 95% CI, 1.1 to 2.5, P = 0.01), as compared to normoxia (87/403 [23%]). In a multivariate analysis, the probability of being exposed to hyperoxia was independently associated with higher in-hospital mortality (adjusted OR, 1.5; 95% CI, 1.02 to 2.4; P = 0.04).

Should we implement this into our practice?

Yes. The available evidence suggests harm with both hypoxaemia and hyperoxaemia. Although a definitive randomized controlled trial is required to answer this question, in the interim, there needs to be a strong rationale to choose to expose a patient to an abnormal partial pressure of oxygen.

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The CLEAN Trial

Mimoz O, Lucet J, Kerforne T, Pascal J, Souweine B, Goudet V, et al. Skin antisepsis with chlorhexidine–alcohol versus povidone iodine–alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): an open-label, multicentre, randomised, controlled, two-by-two factorial trial. Lancet 2015 Nov 21; 386: 2069–77

Study synopsis

This was a multi-centre, randomised trial with a two-by-two factorial design performed in eleven French ICUs. Its primary aim was to investigate the difference in catheter-related infections using 2% chlorhexidine – 70% isopropyl alcohol versus 5% povidone iodine – 69% (ethanol) alcohol as a skin antiseptic.

Consecutive patients admitted to the adult ICU and who required at least one of an arterial, haemodialysis, or central venous catheter for a minimum of 48 hours were eligible, unless they had a known intolerance to the study antiseptics or required an impregnated catheter. Randomisation occurred via a centralized web based system and patients were placed in a 1:1:1:1 grouping in permuted blocks of eight to one of the four treatment groups. The randomization process was also stratified for each ICU.

After randomization, skin preparation was assigned to either chlorhexidine–alcohol or povidone iodine–alcohol with or without scrubbing of the skin with detergent before antiseptic application. Scrubbing of the skin was performed by a nurse using sterile gauze soaked with antiseptic detergent and applied for at least 15s, rinsed with sterile water, and dried with sterile gauze before the line was inserted in a standardized fashion and with a further application of study antiseptic solution. All line insertions were performed in compliance with international guidelines using full sterile barrier precautions.[1] The same catheters and dressings were used throughout the study. Subsequent manipulation of lines and access ports was done with gauze moistened with the same solution used for line insertion. Infective complications were sought by daily catheter site inspection, simple quantitative broth dilution culture of the line tip and blood cultures taken dependent on clinical signs or suspicion of an infection. Paired cultures were taken if the line was left in situ on ICU discharge.

The primary outcome was the incidence of catheter-related infection, defined as either a catheter-related sepsis without bacteraemia or a catheter-related blood stream infection (CR-BSI). A catheter-related sepsis without bacteraemia was defined as a combination of fever or hypothermia, catheter colonisation, with resolution of symptoms within 48 hours after catheter removal and without any change in antimicrobial therapy, or with presence of pus at the catheter insertion site. A CR-BSI was defined as a combination of fever or hypothermia, one or more positive peripheral

blood cultures drawn 48 hours before or after catheter withdrawal, isolation of the same organism from the colonised catheter or from the catheter insertion site, or a blood culture differential time-to positivity of 2 hours or more. If the organism was a potential skin contaminant, two peripheral cultures were required. Secondary outcomes were the incidence of catheter colonisation, CR-BSI, skin insertion-site colonisation, ICU mortality and length of stay and safety outcomes, including skin status.

Based on previous work, it was hypothesized the chlorhexidine-alcohol solution would reduce CR-BSI by 50%. Based on a 5% incidence of catheter infections in the povidone iodine-alcohol group, and using an intraclass correlation within patients of 0·02, a two-sided α risk of 5%, and power of 80%, a sample size of 4,512 catheters was needed, which approximated to 2,256 patients. Analyses were performed in an intention-to-treat manner.

A total of 5,159 catheters (2,446 arterial, 2,155 central, and 558 dialysis lines) in 2,546 patients were included. 1,181 patients (2,547 catheters) were randomised to chlorhexidine–alcohol (594 patients with scrubbing, 587 without) and 1,168 patients (2,612 catheters) to povidone iodine–alcohol (580 patients with scrubbing, 588 without). Baseline characteristics were similar in the two groups. Chlorhexidine–alcohol was associated with a significantly lower incidence of catheter-related infections (0·28 vs 1·77 per 1000 catheter-days; HR, 0·15; 95% CI, 0·05 to 0·41; P = 0·0002), fewer CR-BSIs (0·28 vs 1·32 per 1000 catheter-days; HR, 0·21; 0·07 to 0·59; P = 0·003) and fewer colonised catheters (3·34 vs 18·74 per 1000 catheter-days; HR, 0·18; 0·13 to 0·24; P < 0·0001). Scrubbing was not associated with a significant difference in catheter colonisation (P = 0·3877). When central venous catheters were analysed, the treatment effect was only observed in the incidence of colonization and not for infectious complications. No systemic adverse events were reported, but severe skin reactions occurred more frequently in chlorhexidine alcohol group (3% vs 1%; P = 0·0017).

Critique

Arterial and central venous assess insertion is an almost universal procedure performed in the ICU. However, catheter insertion can lead to blood stream infections, which are associated with increased morbidity and mortality.[2,3] Multiple factors have been identified in international guidelines that may affect the subsequent catheter infection rates, including hand hygiene and disinfection of the skin, use of catheters coated with antimicrobial or antiseptic agents, catheter dressings and insertion site.[4,5] However, the importance of each recommendation over another is unknown. In terms of skin disinfection, some guidelines[4,5] recommend chlorhexidine and alcohol solutions, whilst others[6] recommend either chlorhexidine or povidone iodine solutions. There is some evidence[7-9] that chlorhexidine solutions might be superior to povidone iodine, however these trials used different chlorhexidine solutions and hence the results are difficult to compare. In addition, this trial incorporated skin scrubbing which has been shown to

decrease skin bacterial load[10] but has not been tested in a large trial and is not mentioned in the previous guidelines. By testing a commercially available chlorhexidine - alcohol solution against another common solution, povidone iodine - alcohol, this trial addressed an important part of the bundles commonly recommended to prevent catheter-related infections.

This study has multiple strengths. It is the largest randomised multi-centre trial investigating the use of 2% chlorhexidine – 70% isopropyl alcohol versus 5% povidone iodine – 69% (ethanol) alcohol as a skin antiseptic. The power calculation was based on a 50% reduction in infection rates, which seems optimistic, but is consistent with the reductions found in a previously published meta analysis.[11] The recruitment process was impressive (2,546 eligible patients, with 2,349 enrolled) with few exclusions (21 patients, mainly due to futility of treatment), and a good mix of both medical and surgical patients aiding the generalisation of results. Randomisation successfully ensured an equal distribution of patients with similar baseline characteristics in each of the four groups, limiting the risk of confounding variables. In terms of the intervention, training and explanatory posters were provided, in addition to a research assistant at each site. The diagnosis of catheter-related infections can be difficult, and there are multiple techniques described. Another positive of this trial is the diagnostic procedures used have been recommended by international guidelines.[12] Finally an informative economic analysis was performed.

There are some limitations in this trial. Blinding of the clinical team was not possible, as the solutions had a different appearance. However, the microbiologists performing skin and catheter cultures were blinded and all suspected cases of catheter-related infections were reviewed by blinded assessors, with diagnoses based on detailed established definitions. The lack of blinding in the clinical team is therefore reasonably mitigated. Training was provided and although there was less monitoring of compliance with the protocol, each unit had a research assistant and adhered to catheter management guidelines. The investigators collected data on a huge range of potential confounding variables, although the use of ultrasound for catheter insertion was not reported. It is unclear whether ultrasound affects infection rates,[13] and due to the randomisation process, it is unlikely this had a major effect. Finally, despite an impressive reduction in infections with all catheters, the study was unable to show an effect in central venous catheters, which are thought to be responsible for the majority of catheter-related infections.[4] A suitable powering for this subgroup would have made the trial universally applicable. For possibly the same reason, the trial failed to show any difference in clinical outcomes. However, given the association been these serious infections and adverse outcome, it may not be unreasonable to assume a larger trial may have clinical and economic benefits.

The investigators concluded the results of this trial can be reasonably generalised to the

critically ill population for short term catheters. However, further work is required to establish the most beneficial concentration of chlorhexidine and alcohol. With increasing use of these solutions, adverse reactions, although infrequent in this trial, may become more problematic.

Where it sits in the body of evidence

- In a randomised trial with 668 combined arterial and central venous catheters, patients were randomised to 10% povidone-iodine, 70% alcohol, or 2% aqueous chlorhexidine disinfection of the site before insertion, and for site care every other day thereafter.[7] Chlorhexidine was associated with the lowest incidence of local catheter-related infection (2.3 per 100 catheters vs 7.1 and 9.3 for alcohol and povidone-iodine, respectively; P = 0.02). Of the 14 infusion-related bacteraemias, 1 was in the chlorhexidine group and 13 were in the other two groups (OR, 0.16; P = 0.04).

- A brief 15 month trial in a surgical and trauma population randomised patients to a solution of 0.25% chlorhexidine gluconate, 0.025% benzalkonium chloride, and 4% benzyl alcohol or 10% povidone iodine for insertion and care of both central and arterial catheters.[8] The rate of central venous catheter colonization and catheter-related sepsis were significantly lower in the chlorhexidine group (8 vs. 31 [RR, 0.3; 95% CI, 0.1 to 1; P = 0.03] and 5 vs. 19 [RR, 0.3; 95% CI, 0.1 to 1; P = 0.02], respectively). Arterial line colonisation was also significantly lower, but not arterial line infections. The 0.25% chlorhexidine solution seemed to have more activity in preventing catheter colonizations and catheter-related sepsis due to Gram-positive bacteria.

- In a multi-centre trial, 403 adults were randomised to skin prep with either an aqueous solution of 10% povidone-iodine or an alcoholic solution of 0.5% chlorhexidine before phlebotomy.[14] Of 2,041 blood cultures, chlorhexidine reduced the incidence of blood culture contamination more than povidone-iodine (14 of 1019 cultures [1.4%] compared with 34 of 1022 cultures [3.3%]; OR, 0.40; 95% CI, 0.21 to 0.75; P = 0.004).

- A further multi-centre, randomized controlled trial compared 0.5% tincture of chlorhexidene with 10% povidone-iodine as cutaneous antiseptic solution for central venous catheter insertion.[15] Two hundred and forty-two central venous catheters were inserted. Documented catheter-related bacteraemia rates were not significantly different; 4.6 cases per 1,000 catheter-days in the chlorhexidine group (n = 125) and 4.1 cases per 1,000 catheter-days in the povidone-iodine group (n = 117). Significant catheter-tip colonisation occurred in 24 (27%) of 88 patients in the povidone-iodine group and in 31 (34%) of 92 patients in the chlorhexidine group, with the difference being non-significant.

- In a multi-centre randomised trial, consecutive medical ICU patients had catheters inserted and cared for with either 10% aqueous povidone-iodine solution or 5% povidone-iodine - 70% ethanol in blocks of three months over a 12 month period.[16] The incidence of catheter colonization was significantly lower in the alcoholic povidone-iodine solution group than in the aqueous povidone-iodine solution group (RR, 0.38; 95% CI, 0.22 to 0.65, P 0 < 0.001), as so was the incidence of catheter-related infection (RR, 0.34; 95% CI, 0.13 to 0.91, P 0 < 0.04). Catheter-related bacteraemias were similar in both groups.

- In a randomised trial 5% povidone-iodine in 70% ethanol was compared with a combination of 0.25% chlorhexidine gluconate, 0.025% benzalkonium chloride, and 4% benzylic alcohol for central venous line insertion and care. Of 538 catheters randomized, 481 (89.4%) produced evaluable culture results. Compared with povidone-iodine, the chlorhexidine-based solution was associated with a 50% decrease in the incidence of catheter colonization (11.6% vs 22.2%; P = 0.002), and with a trend toward lower rates of catheter-related bloodstream infection (1.7% vs 4.2%; P = 0.09).[17]

- In a further single centre prospective, randomized controlled trial in a mixed ICU population, 10% aqueous povidone-iodine (aqueous PI), 2% aqueous chlorhexidine gluconate (aqueous CG), and 0.5% alcoholic chlorhexidine gluconate (alcoholic CG) were compared.[18] A total of 631 catheters were included in the study (194 PI group, 211 CG group, and 226 alcoholic CG group). The incidence of catheter colonization was significantly lower in the alcoholic CG than in the aqueous PI group (14.2% vs 24.7%; RR, 0.5; 95% CI, 0.3 to 0.8; P < 0.01); it was also significantly lower in the aqueous CG group than in the aqueous PI group (16.1% vs 24.7%; RR, 0.6; 95% CI, 0.4 to 0.9; P = 0.03). There were no significant differences between the aqueous CG and the alcoholic CG groups. Bacteraemias were similar for all three groups.

- Finally, in an observation trial completed over two years, alcoholic povidone-iodine and chlorhexidine-based antiseptics were compared. The study included 806 central venous catheters (chlorhexidine n = 371). Upon switching from alcoholic povidone to chlorhexidine, surveillance recorded a significant reduction in colonisation incidence/100 catheter days (1.12 vs. 1.55; P = 0.041), nonsignificant differences concerning CVC-related infection incidence/100 catheter days (0.28 vs. 0.26; P = 0.426), and a nonsignificant reduction in CVC-related bacteremia/100 catheter days (0.14 vs. 0.30, P = 0.052).

Should we implement this into our practice?
Yes. Alcoholic chlorhexidine consistently reduces line contamination rates and in this study reduced catheter-related infections.

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Dulhunty JM, Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C et al. A Multicenter Randomized Trial of Continuous versus Intermittent β-lactam Infusion in Severe. Am J Respir Crit Care Med 2015 Dec 1; 192; 11:1298–1305.

Study synopsis

This was a prospective, multi-centre, double-blind, double-dummy, randomised trial performed in 25 ICUs (17 in Australia, 7 in New Zealand and 1 in Hong Kong). The primary aim was to investigate the effect of continuous versus intermittent β-lactam antibiotic infusions on intensive care free days after 28 days.

Patients admitted to the adult ICU who met criteria for severe sepsis, and who were commenced on a β-lactam antibiotic (namely piperacillin–tazobactam, ticarcillin–clavulanate, or meropenem), were eligible for recruitment. Patients were excluded if they had received treatment for more than 24 hours, were under 18 years, pregnant or had an allergy to the study drugs. Recruited patients were randomised to receive the β-lactam antibiotic by either continuous infusion or intermittent infusion over 30 minutes, in addition to an infusion of 0.9% sodium chloride administered as a double-dummy placebo. Randomization was stratified by site on a 1:1 basis. Participants, treating clinicians, and study investigators undertaking assessments or data collection were masked to the treatment allocation.

All participants received a loading dose before commencement of the blinded study drug infusion. Study drug administration was continued for the treatment course or until ICU discharge. A change between the three study antibiotics was allowed and patients could be de-escalated to flucloxacillin, but administration remained as per the allocated group by either infusion or intermittent bolus. The total drug administered remained the same in each group and was decided by the treating physician. Concomitant antibiotic therapy was allowed. Blood cultures were performed before antibiotic administration and then daily for 48 hours after negative samples.

The primary outcome was alive ICU-free days, determined at day 28 after randomization. Secondary outcome measures included 90-day mortality, clinical cure assessed at 14 days after discontinuation of antibiotics, organ failure free days at 14 days and duration of bacteraemia. Adverse events were assessed and recorded.

The sample size calculation was based on previous data, and estimated that 420 patients were required to achieve 90% power to detect a 3 day difference in the primary outcome. Analysis was based on the intention-to-treat principle for primary end points,

in addition to a planned modified intention-to-treat analysis conducted in eligible patients who received a study drug and an a priori per protocol analysis in those who received 3 or more days of a study drug.

A total of 432 patients were enrolled with a median age of 64 years and an APACHE II score of 20. Baseline characteristics were similar between groups. In particular, the source of infection, organ dysfunction and requirement for renal replacement therapy were well matched. Median open label antibiotic administration prior to randomization was 13 hours for the continuous and 12 hours for the intermittent group The median duration of the blinded study drug was 3.2 days [IQR, 1.9 to 6.0] for the continuous group and 3.7 days [IQR, 1.9 to 5.9] for the intermittent group. The median total course of β-lactam antibiotic therapy was 5.3 days [IQR, 2.9 to 7.7] for the continuous group and 5.0 days [IQR, 3.1 to 8.0] for the intermittent group. The choice of antibiotic was similar in both groups, with piperacillin–tazobactam administered in 69.3% and 71.4% of patients, respectively. A change in antibiotic occurred in a similar number of patients (9.4% continuous vs 11.8% intermittent), mainly escalation to meropenem.

There was no difference in the primary outcome of being alive ICU-free days at day 28; 18 days in the continuous group (IQR, 2 to 24) versus 20 days in the intermittent (IQR, 3 to 24) (P = 0.38). There were no differences in the secondary outcomes or after the pre designed statistical analysis.

Critique

Survival from sepsis depends on early initiation of effective antimicrobial treatment.[1] However, less is understood regarding the optimal dose and administration modalities, as these depend on several factors, including the pathogen, the host, and the antibiotic itself. β-lactam and carbapenems are time dependent antibiotics with maximum bacterial killing well above the minimum inhibitory concentration[2] (MIC), and therefore the time the free drug is above the MIC is important to consider when dosing. For many antibiotics dosing is based on weight with consideration to liver and renal function; however, in critical illness there are changes in drug binding, volumes of distribution and drug clearance, making dosing more complicated.[3,4] Antibiotic infusions may provide more stable drug levels above the MIC[5,6] and therefore better clinical outcomes. There have been prospective randomised human studies which demonstrated clinical outcome advantages of continuous infusion,[7,8] although meta analyses have not been able to demonstrate survival or clinical cure benefits.[9,10] There is clearly a pressing need for further research in this crucial aspect of care of the critically ill septic patient.

This study has multiple strengths. It is a large randomised multi-centre trial with a high percentage of patients with severe sepsis. The number of patients was based on a suitable power calculation, although retrospectively, perhaps a reduction in the primary outcome of three days may have been overly ambitious. The trial design was

appropriate. Recruitment and randomisation produced a heterogenous critically ill population with similar baseline characteristics. The trial was inventively blinded from the clinical team using dummy infusions and further blinding of the microbiologists minimised the risk of bias. The statistical analysis was on an intention-to-treat principle, with sensitivity analyses, and the groups were adequately sized even after exclusions post randomisation. The trial also monitored for adverse drug events (which were low). Perhaps monitoring for hospital-acquired infections may have also been useful. Finally, the end points of the trial were clinically relevant.

As with any trial there are some limitations. The trial screened a large number of patients and excluded 83%, mainly due to administration of antibiotics for more than 24 hours, but also a large number of patients were unable to be recruited due to an inability to randomise. It is unclear if this had a meaningful effect on the trial, as the population recruited appears representative of the general intensive care population. Another limitation, acknowledged by the investigators, was the low rates of positive blood cultures (19%), leading to the question whether the patients actually had infections or that the pathogens were easily susceptible to antibiotics previously administered. The pathogens cultured (27% Gram positive versus 73% Gram negative) were almost universally susceptible to the study drugs and bacteraemia times were short. This may also explain the short duration of antibiotics (approximately five days in both groups). When micro-organisms are highly susceptible, the probability of not reaching the required MIC target using conventional dosing is probably small, thereby limiting the study's ability to show a treatment difference. Another confounding factor may have been the inclusion of patients on renal replacement therapy. These patients may have reduced drug elimination and again diluting the effect of the intervention. Recording drug levels may have been beneficial. The trial was not powered for mortality.

The investigators concluded outcomes in a heterogeneous population were equivalent for intermittent versus continuous infusions. Perhaps targeting more resistant pathogens or particular sub populations may have more positive outcomes.

Where it sits in the body of evidence

- Intermittent and continuous infusions of ceftazidime were compared for the treatment of nosocomial pneumonia in 31 critically ill trauma patients.[11] Despite altered volumes of distribution and clearance, the time above the MIC was ≥ 92% of the dosing interval for all patients. Treatment outcomes were similar between the two groups.

- In a prospective, randomized pilot study in 35 ICU patients with nosocomial pneumonia, ceftazidime was administered either as a 3 g/day continuous infusion or an intermittent infusion of 2 g every 8 h.[12] Clinical efficacy, defined as cure/improvement was similar between groups (infusion versus bolus) 94% (16/17) versus 83% (15/18),

while microbiological response was also comparable 76% (10/13) versus 80% (12/15).

- A prospective, randomised, parallel group study was carried out in 50 critically ill patients with severe pneumonia (n = 41) or bacteraemia (n = 9).[13] They received cefepime 4 g/day, either as a continuous infusion or intermittent administration, in combination with amikacin. Mechanical ventilation, clinical outcome and bacteriological eradication did not significantly differ between the two groups. The time above MIC (t > MIC) was not significantly higher in the infusion group (100 ± 0%) than in the bolus group (90 ± 11%), however t > five-fold MIC (100 ± 0%) was significantly higher (82 ±25%) (P = 0.01), suggesting a potential treatment benefit.

- Ten patients with intra-abdominal infection were randomised to meropenem at a daily dose of 0.5 g in 3 divided doses by intravenous infusion over 3 hours or bolus dose.[14] There were significant decreases in the SIRS scores at 96 hours after the drug administration, however, there were no significant differences in the temperature, WCC or CRP between the two groups.

- In a larger randomized, multi-centre, open-label study, 262 hospitalized patients with complicated intra-abdominal infections were randomised (1:1) to piperacillin-tazobactam 12 g/1.5 g administered continuously over 24 h or 3 g/0.375 g administered over 30 min intermittently every 6 hours for 4 to 14 days.[15] Among 167 clinically evaluable patients, 86.4% and 88.4% of the patients treated with the continuous infusion and the intermittent infusion, respectively, were clinically cured or improved (P = 0.817). Bacteriological success was observed in 83.9% and 87.9% of patients (P = 0.597) in the two groups, respectively, with no differences in bacteriological response by pathogen were noted.

- In this prospective, randomised controlled trial, 40 septic critically ill patients received piperacillin, either continuously (2 g intravenously, [i.v.]) over 0.5 hours as a loading dose followed by 8 g i.v. daily over 24 hrs [n=20]) or as an intermittent infusion (3 g i.v. every 6 hrs over 0.5 hrs [n=20]).[16] Change in APACHE II scores from baseline at the end of the second, third and fourth days, respectively, were 4.1, 5.1 and 5.2 for continuous and 2.0, 2.6 and 2.8 for intermittent infusion (P ≤ 0.04). Considering minimum inhibitory concentrations (MICs) of 16 microg/mL and 32 microg/mL, the percentage of time for which piperacillin plasma concentrations were higher than the MIC (%T>MIC) was calculated for each patient in the two groups. For MICs of 16 microg/mL and 32 microg/mL, %T>MIC in the continuous infusion group was 100% and 65% of the dosing interval, respectively; in the intermittent infusion group, %T>MIC was only 62% and 39% of the dosing interval.

- A randomized, controlled prospective nonblinded study was performed in 93 consecutive hospitalized patients requiring antibiotics for acute exacerbations of

chronic obstructive pulmonary disease.[17] Forty-seven patients received 2 g of cefotaxime intravenously over 24 h plus a loading dose of 1 g, and 46 patients were given the drug intermittently (1 g three times daily). Clinical cure was achieved in 93% (37/40) of those receiving continuous administration versus 93% (40/43) of patients receiving the drug intermittently (P = 0.93). In microbiologically evaluable patients, criteria such as 70% of treatment time with antibiotic concentrations ≥ MIC (continuous infusion100% vs. intermittent administration 60% of patients) and/or ≥ 5 x MIC (continuous infusion 100% vs. intermittent administration 55% of patients) were significantly better following continuous administration (P < 0.01).

- In an open-label, pilot study, 57 septic patients were randomized to receive 2 g of ceftriaxone by once-daily bolus or by 24 hour continuous infusion.[7] Intention-to-treat analysis found no significant differences for clinical response (P = 0.17), clinical cure (infusion 13/29 versus bolus 5/28; adjusted OR, 3.74; 95% CI, 1.11 to 12.57; P = 0.06), bacteriological response (P = 0.41) and bacteriological cure (infusion 18/29 versus bolus 14/28; adjusted OR, 1.64; 95% CI, 0.57 to 4.70; P = 0.52). Logistic regression analysis associated continuous infusion of ceftriaxone with an improved outcome (adjusted OR, 22.8; 95% CI, 2.24 to 232.3; P = 0.008).

- In a cohort study of patients who received piperacillin-tazobactam therapy for a Pseudomonas aeruginosa infection over a four year period,patients were initially treated with intermittent infusions of piperacillin-tazobactam (3.375 g intravenously for 30 min every 4 or 6 hours).[18] After 24 months, all patients received extended infusions of piperacillin-tazobactam (3.375 g intravenously for 4 hours every 8 hours). A total of 192 patients were treated (102 bolus, 92 infusion). In the sicker patients with an APACHE score greater than 17, 14-day mortality rate was significantly lower among patients who received infusion therapy (12.2% vs. 31.6%; P = 0.04), and median duration of hospital stay was significantly shorter for these patients (21 days vs. 38 days; P = 0.02).

- In this randomised trial 240 patients admitted to ICU with severe infections were randomized to a loading dose of 2 g of meropenem followed by a continuous infusion of 4 g of meropenem over 24 hours or 2 g of meropenem over 30 minutes every 8 hours.[19] Clinical cure was comparable between groups (83.0% patients in the infusion vs. 75.0% patients in the bolus group; P = 0.180). Microbiological success rate was higher in the infusion group as opposed to the bolus group (90.6% vs. 78.4%; P = 0.020). Multivariate logistic regression identified continuous administration as an independent predictor of microbiological success (OR, 2.977; 95% CI, 1.050 to 8.443; P = 0.040). Meropenem-related ICU stay was shorter in the infusion group compared to the bolus group (10 vs. 12 days; P = 0.044) as well as shorter duration of meropenem therapy (7 days vs. 8 days; P = 0.035) and lower total dose of meropenem (24 grams vs. 48 grams; P < 0.0001).

- A prospective, double-blind, randomized controlled trial of continuous infusion versus intermittent bolus dosing of piperacillin-tazobactam, meropenem, and ticarcillin-clavulanate was conducted in 5 ICUs.[8] Sixty patients were enrolled with 30 patients each allocated to the intervention and control groups. Plasma antibiotic concentrations exceeded the MIC in 82% of patients (18 of 22) in the continuous arm versus 29% (6 of 21) in the intermittent arm (P = 0.001). Clinical cure was higher in the continuous group (70% vs 43%; P = 0.037), but ICU-free days (19.5 vs 17 days; P = 0.14) did not significantly differ between groups. Survival to hospital discharge was 90% in the continuous group and 80% in the intermittent group (P = 0.47).

Should we implement this into our practice?
No. Although there maybe a theoretical benefit, and in some studies pharmacokinetic benefits, there is no convincing clinical benefit. There is currently not enough evidence to suggest a benefit for continuous over intermittent dosing in critical care.

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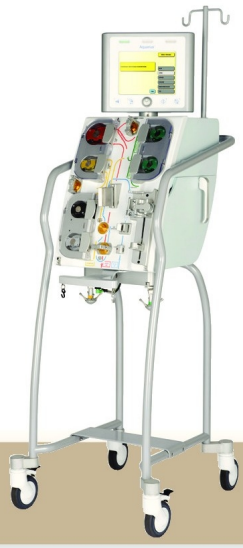

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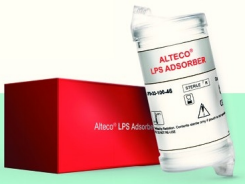

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The CITRATE Trial

Gattas DJ, Rajbhandari D, Bradford C, Buhr H, Lo S, & Bellomo R. A Randomise Controlled Trial of Regional Citrate Versus Regional Heparin Anticoagulation for Continuous Renal Replacement Therapy in Critically Ill Adults. Critical Care Medicine 2015; 43:1622–1629.

Study synopsis

This was a multi-centre, randomised controlled trial performed in Australia and New Zealand, aiming to assess the effect on functional filter life of two methods of regional circuit anticoagulation, citrate and calcium versus heparin and protamine.

Critically ill patients who required renal replacement therapy for acute renal failure were eligible for recruitment. The intervention randomized patients to either regional citrate anticoagulation with maintenance of systemic normocalcaemia or regional heparin anticoagulation with protamine reversal to avoid systemic anticoagulation. Differences existed between sites in terms of machines and delivery of continuous renal replacement therapy (CRRT), however, within each site, efforts were made to standardise determinants of circuit life with regard to modality, pre or postdilution, and starting flow rates. Circuit changes were scheduled after 72 hours as per manufacturer recommendations. All decisions regarding the use of renal replacement therapy and the delivery were at the discretion of the treating team. The reason for discontinuation of the renal replacement therapy was recorded by the treating team and was deemed due to clot if the transmembrane pressure was greater than 300 mmHg, there was visible clot or the pump was unable to rotate due to clot. Other reasons for discontinuation were recorded in free text and a decision retrospectively made by blinded intensivists as to whether clotting was implicated. Study interventions were discontinued when CRRT was discontinued indefinitely.

A sample size of 220 patients had 80% power calculation to detect a difference in mean circuit survival of 4 hours. The primary outcome was functional circuit life. The study examined several secondary outcomes including the effect on inflammatory markers, red cells transfusion requirements, duration of CRRT (hours), ICU length of stay, and hospital mortality.

A total of 212 patients were randomized, although 8 patients did not receive the intervention. Baseline characteristics were similar, although the citrate group had relatively more emergency department admissions (23% vs 36%) and a higher percentage of severe sepsis patients (45% vs 32%). In total 857 circuits (390 in citrate group and 467 in heparin group) were used during the study period with the median number of two circuits per patient.

Overall for patients receiving citrate anticoagulation, the median circuit life of the first circuit was 39.2 hours (95% CI, 32.1 to 48.0 hours) versus a median heparin circuit life of 22.8 hr (95% CI, 13.3 to 34.0 hours; log rank P = 0.0037; 204 circuits). Furthermore, significantly more circuits clotted in the heparin group (66.4%) compared to the citrate group (57.9%) (P < 0.02). In the circuits that clotted, the median circuit life was 16.5 hours (IQR, 21.1 hours) in the citrate group compared with 11.8 hours (IQR, 14.3 hr) in the heparin group (P < 0.0001). There were no significant differences in the secondary outcomes recorded.

Critique

Acute kidney injury is common in critically ill patients and is associated with morbidity and mortality.[1] There have been several recent large studies investigating the intensity of renal replacement[2,3] and although high intensity dosing does not appear to convey survival benefit, clotting of circuits still has the potential to prevent adequate dosing.[4] Sufficient anticoagulation without excessive bleeding is targeted to maintain filter patency. Traditionally, systemic anticoagulation with unfractionated heparin has been widely used, however, systemic anticoagulation may increase bleeding risk and is contraindicated in a variety of critically ill patients. Such issues have lead to the use of regional anticoagulation of the circuit. Citrate anticoagulation use been compared to systemic heparin in several trials with conflicting results,[5-11] however, its use is still recommended in clinical guidelines.[12] Despite the widespread use of heparin/protamine in a major renal dosing trial, this is the first trial to compare regional circuit anticoagulation with heparin and protamine versus citrate and calcium.

This is an important trial with potential beneficial clinical and economic outcomes. It has many commendable strengths. It was a multi-centre randomised trial, although 74% of the patients were from two centres. This was a large study in terms of patient numbers (212 patients), circuits used (857 circuits) and time on renal replacement therapy (cumulative 16,296 hours). The patient population was relatively well matched (there were, however, more severe sepsis patients in the citrate group (45/105 vs 32/107). The recruited patients also reflected a severely unwell population (mean APACHE II scores were 25.6 in the citrate group and 25.0 in the heparin group), with high percentages of patients requiring mechanical ventilation (77% vs 75%) and inotrope therapy (68.4% vs 66.4%). Once randomised the intervention was delivered to the vast majority of patients, with only eight not receiving the designated intervention. There were no patients lost to follow up in either group. The trial also examined other factors that could have affected filter clotting, including coagulation screens and platelet counts, catheter insertion sites, renal replacement modality and blood flow rates. The groups were again well matched, although the heparin group had high starting blood flow rates.

There are also some weaknesses. While the trial screened over 20,000 patients and excluded the majority because renal replacement was not required, the protocol also

excluded a large number of patients (1,219) because they did not meet inclusion criteria. It was not clear if these patients received renal replacement therapy. This could question the generalisibilty of the results. Although the patient population had relatively high APACHE II scores there was a large population admitted electively after surgery (almost one third of patients). This may not reflect the usual critically ill patient population. The trial intervention was unblinded and relied on self reporting of reasons for discontinuation of therapy, which could introduced bias. The data analysis was, however, performed by blinded statisticians. The Investigators state the pragmatic acceptance of variation in CRRT protocols added to the generalisability of the results, however, although all the sites had protocols for both citrate/calcium and heparin/protamine anticoagulation, there is no evidence of each centre's experience with each technique. There is a potential the results could have been affected by the ability of a centre to adequately perform each technique, although the relatively prolonged filter life in both groups would suggest this was not particularly relevant. Finally, although the study's main outcome was filter life, the investigators examined and reported a null effect on patient outcomes, when it was not powered to detect a difference.

The investigators concluded regional citrate and calcium anticoagulation prolongs CRRT circuit life compared with regional heparin and protamine anticoagulation and was associated with fewer adverse events. However, as the study was not powered to detect clinical differences perhaps an economic evaluation would have been useful in this large trial.

Where it sits in the body of evidence

- In a small prospective, randomized cross over, single centre trial, ICU patients with acute renal failure requiring continuous renal replacement therapy were randomized to anticoagulation with heparin or trisodium citrate.[5] Patients requiring another CVVH run received the other study medication. Forty-nine circuits were analysed: 23 with heparin and 26 with citrate. The median lifespan with citrate was 70 hours (IQR, 44 to 140) versus 40 hrs (IQR, 17 to 48) with heparin (P = 0.0007). One major bleed occurred with heparin and one episode of metabolic alkalosis was noted with citrate. Transfusion rates were lower with citrate (P = 0.0008).

- In a further small randomised trial 30 critically ill subjects requiring CRRT were randomly assigned to receive regional citrate or systemic heparin anticoagulation.[6] Seventy-nine filters were used; the median haemofilter survival time was 124.5 hours (95% CI, 95.3 to 157.4) in the citrate group, which was significantly longer than the 38.3 hours (95% CI, 24.8 to 61.9) in the heparin group (P < 0.001). After adjustment for antithrombin-III levels and illness severity score, the relative risk of haemorrhage with citrate anticoagulation was significantly lower than with heparin (RR, 0.14; 95% CI, 0.02 to 0.96, P = 0.05).

- In a prospective observational cohort study, 87 patients with acute renal failure requiring CRRT were identified.[13] Fifty-four were initially treated with citrate, 29 with heparin, and 4 with saline flushes. Citrate and heparin were used in 212 (66%) and 97 (30%) of filters for 8,776 and 2,651 hours of CRRT, respectively. Overall median (IQR) filter life span with citrate was significantly greater than heparin (40 [14 to 72] vs 20 [5 to 44] hours, P < 0.001). The median time to spontaneous filter failure was significantly greater with citrate compared with heparin (>72 vs 33 hours; P < 0.001). No patient required elective discontinuation for hypernatraemia, metabolic alkalosis, or hypocalcaemia.

- In a randomized controlled cross-over study, 10 critically ill patients with acute renal failure treated with CVVH were randomised to regional heparinisation with protamine or regional citrate anticoagulation.[9] There was no difference in median circuit life; regional heparinisation 13 hours (IQR, 9 to 28) compared to regional citrate anticoagulation 17 hours (IQR, 12 to 19.5) (P = 0.77). There were no episodes of bleeding in either group.

- Critically ill patients requiring CVVH and at low risk for bleeding were randomized to regional citrate anticoagulation (n = 21) or systemic heparin anticoagulation (n = 27). A total of 142 CVVH circuits were analysed. Circuit survival and median clotting-free circuit survival were similar for both groups. No significant adverse metabolic events occurred in the regional citrate anticoagulation group. There was no major bleeding in the citrate group, compared with 10 events in the heparin group (P < 0.01). The number of red blood cell units transfused was significantly higher in the heparin group (0.88 vs 0.43 units/day; P = 0.01).[10]

- In a nonblinded, single-centre trial, adult critically ill patients needing CRRT for acute renal failure and without an increased bleeding risk were randomised to regional anticoagulation with citrate or systemic anticoagulation with nadroparin. Two hundred patients received CRRT as per protocol (97 citrate and 103 nadroparin).[11] Adverse events requiring discontinuation of citrate occurred in two patients (accumulation and clotting) and in 20 in the nadroparin group (bleeding and thrombocytopaenia) (P < 0.001). Bleeding occurred in 6 vs. 16 patients (P = 0.08). Citrate conferred less metabolic alkalosis (P = 0.001) and lower plasma calcium (P < 0.001). Circuit survival was similar. Three-month mortality with intention-to-treat analysis was 48% (citrate) and 63% (nadroparin) (P = 0.03), and per protocol analysis, 45% and 62% (p = 0.02).

- This multi-centre trial randomised 174 mechanically ventilated patients requiring renal replacement therapy for acute renal failure, to either regional citrate anticoagulation or with systemic heparin anticoagulation.[7] Use of citrate resulted in less systemic anticoagulation (P < 0.001), a lower risk of bleeding (P = 0.06) and a longer haemofilter patency 37.5 ± 23 h versus 26.1 ± 19 h (P < 0.001). Abnormalities of calcium occurred

more often with citrate treatment. Mortality was not influenced by the mode of anticoagulation.

- In another multi-centre trial, 139 patients admitted to the intensive care unit requiring CVVH were randomly assigned to citrate (66 patients) or systemic heparin (73 patients).[8] Mortality rates at 28 and 90 days did not differ between groups (P = 1.00 for both) nor did the incidence of renal recovery, 67% in the citrate-treated patients versus 70% in heparin-treated patients (P = 0.82). Heparin was discontinued in 33% of patients and citrate was discontinued in 8% (P < 0.001). Filter survival times were longer for citrate (median 46 versus 32 hours; P = 0.02) resulting in less filters used and less off time within 72 hours. The costs during the first 72 hours were lower with citrate.

Should we implement this into our practice?

Yes. Renal outcome and patient mortality were similar for citrate and heparin-based anticoagulation during CRRT in the critically ill patient. However, citrate has advantages in terms of safety, efficacy and costs and should therefore be considered first choice for anticoagulation in renal replacement therapy in critical illness.

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The FLORALI Trial

Frat J-P, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure. New England Journal of Medicine. 2015 Jun 4;372(23):2185–96.

Study synopsis

This prospective, multi-centre, open-label, randomised, controlled trial compared three oxygen delivery strategies in patients with acute hypoxic respiratory failure. Intensive care patients aged 18 or over were eligible if they met all four of the following criteria; a respiratory rate of > 25 breaths per minute, a PaO_2:FiO_2 ratio of < 300 mmHg following at least 15 minutes of 10 l/min of oxygen, a $PaCO_2$ of < 45 mmHg, and no history of underlying respiratory failure. Exclusion criteria included, but was not limited to, $PaCO_2$ of > 45 mmHg, an exacerbation of asthma or chronic respiratory failure, heart failure or need for urgent intubation.

Patients could be randomised to one of three treatment groups. The method by which these interventions were administered should be noted. The target oxygen saturation in all patients was greater than 92%. The standard oxygen group were commenced on oxygen via a non-rebreather mask at 10 l/min with oxygen subsequently titrated as required. The high-flow nasal oxygen group received humidified oxygen at 50 l/min with a FiO_2 of 1.0 with oxygen concentration titrated to effect. This intervention was continued for at least two days. Non-invasive ventilation was delivered through an ICU ventilator. Pressure support was titrated to achieve a tidal volume of 7-10 ml/kg. The PEEP was set between 2 - 10 cmH_2O. PEEP and oxygen was titrated to achieve saturations > 92%. Patients received non-invasive ventilation for 8 hours per day with each session lasting at least 1 hour. Between session patients received high flow nasal oxygen. Non-invasive ventilation was recommenced if the respiratory rate was > 25 per minute or oxygen saturations were < 92%.

The primary outcome measure was the proportion of patients who required intubation within the first 28 days after randomisation. Criteria were set out to standardise the indications for intubation and included haemodynamic instability, neurological deterioration, or worsening respiratory failure (which required at least two of respiratory rate greater than 40 breaths per minute, excessive work of breathing, copious tracheal secretions, pH < 7.35, or SpO2 < 90% for more than 5 minutes). Secondary outcomes included ICU mortality, 90-day mortality, number of ventilator-free days at day 28 and rate of complications.

The power calculations were based on a 60% intubation rate in the standard-oxygen group. Recruitment of 300 patients would provide an 80% power to show an absolute difference of 20% in the primary measure between the standard-oxygen group and

either of the other two groups. A two-sided alpha level of 0.05 was set.

310 patients were enrolled, 64% of patients had a community acquired pneumonia, 12% had hospital acquired pneumonia, and 77% had a PaO_2:FiO_2 ratio of < 200 mmHg. In the non-invasive group, the following mean settings were observed; pressure support 8 ± 3 cmH_2O, PEEP 5 ± 1 cmH_2O, FiO_2 0.67 ± 0.24 and tidal volume 9.2 ± 3.0 ml/kg. The average duration of non-invasive ventilation was 8 hours each day.

There was no difference in the primary outcome measure of intubation at 28 days; 38% in the high flow nasal oxygen group compared to 47% in the standard oxygen group, and 50% in the noninvasive ventilation group (P = 0.18 for all comparisons). Post hoc analysis of patients with a PaO_2:FiO_2 ratio of < 200 mmHg showed a lower rate in intubation on the high flow nasal oxygen group.

In comparison with the high flow nasal oxygen group, which had a mortality of 13%, a higher 90-day mortality was seen in both the standard oxygen group (HR for death, 2.01; 95% CI, 1.01 to 3.99; P = 0.046) and in the non-invasive ventilation group (HR for death, 2.50; 95% CI, 1.31 to 4.78; P = 0.006). Patients in the high flow nasal oxygen group had a significantly greater number of ventilator free days; 24 ± 8 days, compared to 22 ± 10 in the standard oxygen group and 19 ± 12 in the noninvasive ventilation group (P = 0.02 for all comparisons).

Critique

This is the largest study comparing high flow nasal oxygen with non-invasive ventilation. It has a number of draw backs. 2,506 patients with hypoxic respiratory failure were screened, however, due to strict inclusion and exclusion criteria, only 525 were eligible for inclusion. Each of the 23 participating ICUs saw approximately one eligible patient every five weeks. This raises questions about the generalisability of this study. Although the study was designed to be for patients with acute hypoxaemic respiratory failure, it is borders being a study of pneumonia, as 82% of patients had either community-acquired pneumonia, hospital acquired pneumonia or pneumonia related to immunosuppression.

This study is underpowered due to a lower than expected intubation rate in the standard oxygen group (47% compared to the predicted rate of 60%). It is tempting to over-interpret the large absolute differences in intubation rates. However, a larger trial would be needed to confirm if there is a benefit from high flow nasal oxygen. The lower mortality seen in the high flow nasal oxygen group, which was statistically significant, should also be viewed with caution. The small number of deaths, there were only 13 deaths in the high flow nasal oxygen group, mean that a small change in the number of events in each group could render this non-significant.[1] In addition the confidence intervals were wide. Therefore, this secondary outcome this should be seen as hypothesis generating only.

The comparators to high flow nasal oxygen should be discussed. Patients in the "standard oxygen" group were managed with a non-rebreather mask. This lack of humidification is likely to result in poorer sputum clearance and potentially worsening shunt as a result. Importantly, criteria for intubation included refractory hypoxia and copious tracheal secretions. It is likely humidified oxygen would be standard care for most patients managed in a critical care setting. The British thoracic society guidelines state *"it is reasonable to use humidified oxygen for patients who require high-flow oxygen systems for more than 24 hours."*[2] The counter argument is patients in this group had a lower than anticipated intubation rate.

In the non-invasive ventilation group, patients were allowed breaks. If the SpO_2 was < 92% or the respiratory rate was > 25 breaths per minute during these breaks, non-invasive ventilation was recommenced. This level of hypoxia was close to the SpO_2 of 90% which constituted one of the criteria for intubation. In patients with community-acquired pneumonia, a longer duration of non-invasive ventilation prior to intubation is associated with a higher mortality.[3] Patients with respiratory failure following extubation have a higher mortality when randomised to receive non-invasive ventilation instead of standard medical care. This may be due to a delay in reintubation.[4] It is conceivable the protocol in this paper delayed intubation in some patients. There was no statistically significant difference in time to intubation between the groups (15 hours in the standard oxygen group compared to 27 hours in the other two groups) though the study would not have been powered to detect this. Forty patients in the standard oxygen and high flow nasal oxygen groups received non-invasive ventilation as a rescue therapy. It is difficult to determine the effect this cross over between groups had on delays to intubation in these groups or overall treatment effect.

The pressure support was titrated to achieve a tidal volume of 7-10 ml/kg (it achieved on average 9.2 ml/kg). Tidal volumes of 10 ml/kg have been shown to induce lung injury in mechanically ventilated patients.[5] Although the patients in this trial were not intubated, these tidal volumes may have been injurious.

This study excluded patients with previous respiratory failure or COPD; both groups which have been shown to derive benefit from non-invasive ventilation (even in the setting of normocapnic respiratory failure).[3] This may account for an intubation rate of 50%, which was double that seen in previous studies.[6,7]

In conclusion, the method of administration of non-invasive ventilation may have resulted in poorer than expected outcomes for some of these patients. This should be borne in mind when interpreting the apparent benefit of high flow nasal oxygen.

Where it sits in the body of evidence

- Carrillo and colleagues studied the use of non-invasive ventilation in hypoxic respiratory failure to assess predictors of non-invasive failure and hospital mortality.[3] Of the 184 patients studied, 102 had community acquired pneumonia. Survivors had a shorter duration of non-invasive ventilation than non-survivors (32 ± 24 hours vs. 78 ± 65 hours respectively, P = 0.014). In addition, a longer duration of non-invasive ventilation prior to intubation was associated with a small decrease in hospital survival (adjusted OR, 0.978; 95% CI, 0.962 to 0.995; P = 0.012).

- A multi-centre randomised controlled trial compared non-invasive ventilation with standard medical care in 221 patients with post extubation respiratory failure.[4] There was no difference in re-intubation rates, being 48% in both groups. However, the median time from development of respiratory failure to reintubation was longer in patients assigned to non invasive ventilation (12 hours vs. 2 hours 30 minutes, P=0.02). There was an associated increase in mortality seen in the group assigned to non-invasive ventilation (25% vs.14%; RR, 1.78; 95% CI, 1.03 to 3.20; P = 0.048).

- Determann and colleagues compared mechanical ventilation with tidal volumes of 10 ml/kg with 6 ml/kg in 150 patients without lung injury.[5] The trial was terminated early due to a much higher incidence of induced acute lung injury in the 10 ml/kg group (13.5% vs 2.6%; P = 0.01).

- A randomised controlled trial compared non-invasive ventilation with standard therapy in 236 patients with exacerbations of COPD, a pH 7·25 - 7·35 and a $PaCO_2$ > 6 kPa.[8] Patients randomised to non-invasive ventilation had a reduced need for intubation (15% compared to 27% in the standard therapy group; P = 0·02). Non-invasive ventilation also reduced in-hospital mortality (10% versus 20%; P = 0·05).

- Keenan and colleagues performed a systemic review and meta-analysis examining non-invasive ventilation in exacerbations of COPD. Fifteen trials were assessed, including approximately 650 patients. Non-invasive ventilation was associated with a 28% relative risk reduction in intubation rates (95% CI, 15% to 40%), a reduced length of hospital stay (absolute RR, 4.57 days; 95% CI, 2.30 to 6.83 days), and a 10% relative risk reduction in in-hospital mortality (95% CI, 5% to 15%). The majority of the treatment benefit was derived from patients with severe exacerbations of COPD.[9]

- A multi-centre randomised controlled trial compared standard oxygen therapy, CPAP and non-invasive positive pressure ventilation in 1,069 patients with cardiogenic pulmonary oedema.[10] Patients receiving CPAP or non-invasive positive pressure ventilation were grouped together for some comparisons and termed “non-invasive

ventilation". In comparison to standard oxygen therapy, "non-invasive ventilation" produced statistically significant reductions in dyspnoea scores, hypercapnia, acidosis, and heart rate. However, there was no significant difference in mortality at one week between patients who were managed with standard oxygen therapy compared to those who received "non-invasive ventilation" (P = 0.87). There was no difference in the combined end point of death or need for intubation at one week when patients who received non-invasive positive pressure ventilation were compared to CPAP (P = 0.81).

- A randomised controlled trial compared the effects of high flow oxygen with venturi mask in 105 patients who had a PaO2:FiO2 ratio of < 300 mmHg following extubation.[11] This study was powered to detect differences in PaO_2:FiO_2 ratio, reintubation was a secondary endpoint. Fewer patients required reintubation in the high flow oxygen group (4% vs. 21%; P = 0.01).

- HOT-ER was a single centre study of 322 emergency department patients with hypoxic respiratory failure.[12] Patients were randomised to high flow nasal oxygen or standard oxygen therapy. There was no statistically significant difference in the number of patients requiring intubation in the first 24 hours; 5.5% (95% CI, 2.8 to 10.2%) in the high flow oxygen group compared with 11.6% (95% CI, 7.2 to 18.1%) in the standard oxygen group (P = 0.053).

Should we implement this into our practice?
Maybe. Although evidence supporting high flow nasal oxygen is growing, more work needs to be done to assess it in direct comparison to non-invasive ventilation. In the interim, high-flow nasal oxygen appears to be a reasonable choice in selected groups of patients.

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Hasselqvist-Ax – Early CPR in Out-of-Hospital Cardiac Arrest

Hasselqvist-Ax I, Riva G, Herlitz J, Rosenqvist M, Hollenberg J, Nordberg P, et al. Early Cardiopulmonary Resuscitation in Out-of-Hospital Cardiac Arrest. New England Journal of Medicine. 2015 Jun 11;372(24):2307–15.

Study synopsis

This registry based study from Sweden evaluated the effect of bystander cardiopulmonary resuscitation (CPR) prior to the arrival of Emergency Medical Services (EMS) on 30-day survival rates in out-of-hospital cardiac arrest (OOHA). It also sought to assess the impact of time from collapse to the start of CPR on 30-day survival rates.

The investigators used the Swedish Cardiac Arrest Registry, which includes data from over 90% of OOHA in Sweden. Bystander witnessed cardiac arrests treated by EMS were included from 1st January 1990 to 31st December 2011. From a population of 9.7 million, approximately 3 million Swedish people have been trained in CPR over the last 30 years. Since 1998, when cases of cardiac arrest were called into the EMS, dispatchers provide telephone instructions on how to provide CPR. There is a two tier EMS system. First responder EMS units can carry out basic life support and second responder units can carry out advanced life support. During the study period there were alterations to the resuscitation guidelines in 2000, 2005 and 2010.

Propensity scoring was used to adjust for confounding variables. The factors included in this were: age, sex, cause of cardiac arrest, place of cardiac arrest, initial cardiac rhythm, year of event, time from collapse to call for EMS, EMS response time, and time from collapse to defibrillation in those with an initial shockable rhythm.

The registry included data on 61,781 OOHA cases. 30,381 met the inclusion criteria of being bystander witnessed OOHA, with data recorded on times for the start of CPR and survival outcomes. 51.1% of patients received bystander CPR prior to the arrival of EMS; 48.9% did not. The proportion of patients receiving bystander CPR increased over the study period, from just over one third in 1990 to over two thirds in 2010. As expected, the time to initial CPR was statistically shorter in the bystander CPR group; 4 minutes in the bystander CPR group compared with 11 minutes in the non-bystander CPR group (this being the time of arrival of the EMS) ($P < 0.001$).

When the two groups were compared, there were a number of statistically significant differences. Patients who underwent bystander CPR were younger (69 vs 74 years, $P < 0.001$), less likely to be female (26.8% vs 30.2% $P < 0.001$), and less likely to have collapsed in their own home (55.5% vs 73.2% $P < 0.001$). The character of arrests were also different between the two groups. Patients who had bystander CPR were more

likely to have an initial shockable rhythm (41.3% vs 20.7%, P < 0.001), had a shorter duration before EMS were called (3 min vs 4 min, P < 0.001), but had longer EMS response times (8 min vs 6 min, P < 0.001) and longer duration of collapse to first defibrillation (13 min vs 11 min, P < 0.001). When adjustments were made for other variables, the higher rate of a shockable rhythm persisted in the bystander CPR group.

In the group of patients who received bystander CPR, the 30-day survival was 10.5%, compared to 4.0% for those who did not (P < 0.001). After adjustment for the propensity score (excluding time from collapse to defibrillation), 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). When time from collapse to defibrillation was also included, the difference remained (odds ratio, 2.27; 99% CI, 1.84 to 2.81; P < 0.001). Higher survival was seen in all groups irrespective of age, sex, cause of cardiac arrest, location of cardiac arrest, shockable or non-shockable rhythm, or year of cardiac arrest. There was a marked reduction in 30-day survival, with increasing time before initiation of CPR; survival was 15.6% if there was a 0 to 3 min delay, compared to 0.9% if there was a > 14 min delay.

Critique

This interesting study uses data from a large registry and, as such, is subject to a number of limitations. The investigators comment that approximately 25% of the data were not collected prospectively, but added retrospectively. 10.6% of patients were excluded from this study due to missing data (7.4% for missing witness status, 2.2% for missing data on CPR prior to EMS arrival and 1% for missing data on survival). Cerebral performance scores were only available for approximately 1 in 5 survivors. The authors also acknowledge the time of collapse and CPR start time were often estimated. This reflects the inherent weaknesses of using registry data.

As with any study using registry date, there are often variables or confounding factors that cannot be accounted for, even despite the use of propensity scoring systems. Also, this study can show association, but cannot demonstrate causality. There was an increase in survival in the group of patients that received bystander CPR despite a longer time to arrival of EMS (11 min in total compared to 10 min) and a greater delay before defibrillation (13 min versus 11 min, P < 0.001). However, there are indications that factors other than bystander CPR may have influenced the outcomes in OOHA.

Over the duration of the study, there was a J-shaped survival curve for those who received bystander CPR. In this group, the rate of survival fell for the first decade of the study, from approximately 13% to 6%. Only from 2000 did survival increase, eventually reaching approximately 14%.[1] Of note, two major studies on therapeutic hypothermia were published in 2002.[2,3]

Using the same Swedish Cardiac Arrest Register from 1992 to 2011, Strömsöe and

colleagues examined 59,926 of OOHA, either witnessed or unwitnessed.[4] The 30-day survival increased for all patients during this time period from 4.8% to 10.7% (P < 0.0001). During this time, the greatest survival gains were made in those with shockable rhythms. 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. In 2008-11, of those who achieved ROSC and were hospitalised, 41% were treated with therapeutic hypothermia and 28% underwent percutaneous coronary intervention. The investigators were unable the define the change in use of these interventions over time.[4] This suggests there are factors other then bystander CPR which improve outcomes.

Previous studies have shown bystander CPR is a predictor of shockable rhythm at the time of arrival of EMS, which in turn is a predictor of survival.[5] 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.[6] It is speculated bystander CPR delays the deterioration of a shockable rhythm into a non-shockable rhythm. Data from the Swedish Cardiac Arrest Registry shows a decrease in patients found to be in VF during OOHA over the time period 1992 to 2011 (35% to 25%; P < 0.0001) despite a doubling in the rate of bystander CPR.[4]

The Victorian Ambulance Cardiac Arrest Registry was analysed, including data from 13,448 bystander-witnessed OOHA. [7] It demonstrated bystander CPR was associated with poorer survival to hospital in non-shockable rhythms (adjusted OR, 0.76; 95% CI, 0.59 to 0.97; P=0.03). However, in the Swedish Cardiac Arrest Registry those in a non-shockable rhythm benefited from bystander CPR (odds ratio for survival, 2.12; 95% CI, 1.62 to 2.78). This benefit was of similar magnitude to those who presented with a shockable rhythm (OR for survival, 2.43; 95% CI 2.07 to 2.85).

Overall, this registry-based observational study suggests an association between bystander CPR and improved survival, echoing that of a large Danish registry.[8] There is biological plausibility in this, but evidence points towards a number of confounders in which may influenced these findings.

Where it sits in the body of evidence

- 19,468 patients with OOHA between 2001 to 2010 included in the Danish Cardiac Arrest Registry were examined.[8] 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%) in 2010 (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 (odds ratio, 4.38; 95% CI, 3.17 to 6.06).

- The Swedish Cardiac Arrest Register was interrogated, analysing all OOHA from 1992 to 2011 (n = 59,926).[4] 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 form 4.8% to 10.7% (P < 0.0001). From 2008 to 2011, of those who achieved ROSC and were hospitalised, 41% were treated with therapeutic hypothermia and 28% underwent percutaneous coronary intervention. Ninety-four per cent of survivors had a favourable neurological outcome (cerebral performance category score 1 or 2 at discharge).

- 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.[7] Patients in a shockable rhythm who had bystander CPR had improved survival to hospital discharge (odds ratio, 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 (odds ratio, 0.76; 95% CI, 0.59 to 0.97; P=0.03) after adjustment for arrest confounders.

- A prospective observational study of 873 OOHA patients examined factors influencing the probability VF or asystole.[6] The probability of VF decreased with each minute from time of collapse (OR, 0.92; 95% CI, 0.89 to 0.95), whereas the probability of asystole increased (OR, 1.13; 95% CI, 1.09 to 1.18). Bystander CPR reduced these trends significantly; for VF (OR 0.97, 95%CI, 0.94 to 0.99) and asystole (OR 1.09, 95% CI, 1.05 to 1.13).

- A prospective study of bystander defibrillation involving 105 patients demonstrated a delay of less than three minutes from witnessed collapse to defibrillation was associated with a 74% survival.[9] Those who were defibrillated later than three minutes had a 49% survival.

- A cluster randomised controlled trial looked at the impact of continuous CPR compared with CPR interrupted for ventilation in 23,711 cases of OOHA.[10] Survival to hospital discharge was 9.0% in the continuous CPR group compared to 9.7% in the interrupted CPR group (adjusted difference –0.7%; 95% CI, –1.5 to 0.1; P = 0.07). There was no difference in the rates of neurologically favourable outcome.

- The non-inferiority CIRC trial compared manual CPR with an integrated automated load distributing band CPR (iA-CPR) device in 4,231 patients with OOHA.[11] The chest compression fraction was similar in both groups; 80.4% for iA-CPR and 80.2% for manual CPR. Survival to hospital discharge was 9.4% in the iA-CPR group compared to 11.0% in the manual CPR group (adjusted OR, 1.06; 95% CI, 0.83 to 1.37).

- The cluster randomised PARAMEDIC trial compared outcomes following OOHA in 4,471 patients treated with manual CPR or the mechanical CPR device, LUCAS-2.[12] Only 60% of those in the cluster randomised to receive mechanical CPR device were treated with the LUCAS-2 device. There was no difference in 30 day survival; 6% in the mechanical CPR cluster versus 7% in the manual CPR cluster (adjusted OR 0·86; 95% CI 0·64 to 1·15). Survival with favourable neurological outcomes was lower in the mechanical CPR cluster.

- The LINC trial compared manual CPR following the European Resuscitation Guidelines, with mechanical CPR using the LUCAS device combined with defibrillation during CPR in 3 minute cycles.[13] 2,589 patients with OOHA were enrolled. There was no difference in the primary outcome measure of four-hour survival (23.6% with mechanical CPR and 23.7% with manual CPR). Survival to hospital discharge with a favourable neurological outcome was similar; 8.3% vs 7.8% in the mechanical and manual CPR groups, respectively.

Should we implement this into our practice?
Yes. The body of evidence suggests improved outcomes with bystander CPR, though other factors in OOHA management also play a role.

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Nichol G, Leroux B, Wang H, Callaway CW, Sopko G, Weisfeldt M, et al. Trial of Continuous or Interrupted Chest Compressions during CPR. New England Journal of Medicine. 2015 Dec 3;373(23):2203–14.

Study synopsis

This cluster-randomised crossover trial evaluated the impact of continuous chest compressions during CPR compared with chest compressions interrupted for ventilation on patient survival and neurological outcomes following out-of-hospital cardiac arrest (OOHA).

The intervention group received continuous chest compressions at a rate of 100 per minute, with asynchronous positive pressure breaths at a rate of 10 per minute. The control group received chest compressions interrupted for ventilation at a ratio of 30 compressions to two breaths, with interruptions lasting no longer than 5 seconds. In both groups the airway was maintained with an oropharyngeal airway, with bag-mask ventilation. The use of advanced airway techniques was deferred until at least 6 minutes or until return of spontaneous circulation. Once an advanced airway had been inserted, both groups had continuous chest compressions. In this pragmatic trial, hospital based interventions, including temperature management, were not protocolised.

One hundred and fourteen emergency medical services (EMS) participated in the trial. To be eligible for enrolment patients must have had a non-traumatic OOHA. Cases of cardiac arrest witnessed by the EMS crew were excluded. Other exclusion criteria included, but was not limited to, cardiac arrest due to asphyxia or haemorrhage, and patients treated with a mechanical chest compression device.

The 114 participating sites were grouped into 47 clusters and randomised on a 1:1 basis. Twice per year, each cluster was crossed over to the alternative resuscitation strategy. 23,600 patients were required to achieve a 90% power to detect a 1.3% absolute increase in survival to hospital discharge. This was based on an assumed survival to hospital discharge of 8.1% in the control group. A two-sided alpha level of 0.05 was used.

The primary outcome measure was survival to hospital discharge. Secondary outcomes included neurological function at discharge, assessed using a modified Rankin scale (on a scale from 0 to 6, with a score of ≤ 3 indicating favourable neurological outcome), adverse events and hospital-free survival (number of days alive and permanently out of the hospital in the first 30 days).

A run in phase was used to assess adherence to the protocol. 35,904 patients were screened, 23,711 patients were included in the active enrolment phase and the primary

analysis. The rates of bystander CPR in the intervention cluster was 46.9% and in the control cluster 47.1%. Time from dispatch to first arrival of advanced EMS support was 9.0 ± 5.1 minutes in both clusters. There were no differences in the time to commencing CPR, rates of shockable rhythm, number of shocks given, rates of intubation, or drugs administered.

In keeping with the protocol, the intervention cluster had a greater chest-compression fraction (proportion of each minute during which compressions were given); 0.83 ± 0.14 in the intervention cluster compared to 0.77 ± 0.14 in the control cluster (P < 0.001). The intervention cluster had fewer pauses greater than two seconds (3.8±2.6 vs 7.0±4.3, P < 0.001).

Survival to hospital discharge was 9.0% in the intervention cluster compared to 9.7% in the control cluster (adjusted difference −0.7%; 95% CI, −1.5 to 0.1; P = 0.07). Seven percent of patients in the intervention cluster had a favourable neurological outcome compared to 7.7% in the control group (adjusted difference −0.6%; 95% CI, −1.4 to 0.1; P = 0.09). Hospital-free survival was shorter in the intervention cluster (mean difference, −0.2 days; 95% CI, −0.3 to −0.1; P=0.004). In the per protocol analysis, survival to hospital discharge was significantly lower in the intervention group; 7.6% versus 9.6% (difference -1.3%; 95% CI, −2.5 to −0.1; P = 0.04). However, after adjustment for confounders, this difference was no longer significant (P = 0.38).

Critique

This was an excellent trial with strict quality assurance procedures. Each EMS centre had to undertake a run-in phase, during which prespecified performance and compliance benchmarks were assessed. These benchmarks included adherence to allocated treatment-group, completion of data entry, and availability of CPR-process measures to assess quality of CPR. Only after satisfactory completion of the run in phase was the centre enrolled and allowed to recruit patients. During the study period, monitor defibrillators were used to assess the CPR-process data; this was regularly audited to assess compliance with the allocated treatment and best practice guidelines. In cases where care fell below the desired standard, steps were taken to correct this. EMS centres could be placed on probation or suspended if necessary.

These strict quality assurance procedures are indicative of an excellently conducted trial. The corollary of this is that it may have induced a Hawthorne effect. The chest compression fraction was higher than the recommended minimum of 0.6 by American Heart Association and in keeping with their stated target of 0.8.[1] The chest compression fraction in both groups (0.83 ± 0.14 in the intervention cluster compared to 0.77 ± 0.14 in the control cluster) was similar to those achieved in the CIRC trial which, using a mechanical chest compression device, achieved a chest compression fraction of 0.8.[2] In this trial the survival rates were marginally higher that those in the PARAMEDIC and

LINC trials.[3,4] The high quality CPR in the control cluster may in some part explain the lack of a positive result.

In this trial, there was limited separation between the two groups. In effect, the intervention only lasted for 6 minutes in many patients. After 6 minutes, advanced airway techniques could be used which would result in continuous chest compressions in both groups. 47.8% and 49.2% of the intervention and control clusters respectively were successfully intubated. Although there was a statistically significant difference between the chest compression fraction time, this only equated to the control group having chest compressions for 3.6 seconds less for every minute of CPR. In an observational study examining the effect of chest compression fraction on outcome, only those who required CPR for greater than 20 minutes benefited from higher chest compression fraction.[5] In addition, the rate of protocol adherence was low; less than half of the enrolled patients made it into the per-protocol analysis. This may have diluted any potential treatment effect or indeed harm. When these facts are considered it is understandable why there was no difference in the primary outcome measure.

In the per protocol analysis, survival to hospital discharge was significantly lower in the intervention group (difference -1.3%; 95% CI, −2.5 to −0.1; P = 0.04). After adjustment for measured confounding variables, this difference was non-significant (P = 0.38). There were significant potential confounders in the per-protocol analysis that may have resulted in those within the per-protocol analysis being a self-selected group. For example, there were more patients excluded from the per-protocol analysis in the control cluster. Although the investigators corrected for measured variables, they could not exclude other confounding factors.

In this pragmatic trial there was no control over aspects of post resuscitation care which could affect survival to hospital discharge or neurological outcome. The rates of hypothermia were similar in both clusters, but the use of targeted temperature management to 36°C was not recorded (the TTM trial was published half way through the study recruitment period).[6] The issue of hyperoxia was also not addressed.[7] It is conceivable patients in the continuous chest compression cluster had higher oxygen levels for the period of the intervention, though as previously discussed, the period of intervention that could have resulted in hyperoxia was brief. It is likely interventions which impact on neurological outcome would have been equally distributed between both clusters.

In conclusion, this was a large, well conducted trial. The absence of a difference between clusters is understandable. It once again highlights the poor outcomes in OOHA.

Where it sits in the body of evidence

- An observational study of 414 patients with prolonged out-of-hospital ventricular fibrillation (VF) arrest assessed the effect of chest compression fraction on survival to hospital discharge and neurological outcome.[5] The median chest compression fraction was 0.81. Patients were stratified based on the need for CPR for greater than 5, 10 or 20 minutes. Patients who received CPR with a chest compression fraction of less than 0.81 were compared to those with a chest compression fraction of greater than 0.81. There was no difference in outcomes between the > 5 minutes and > 10 minutes groups. One hundred and fifty-three patients received CPR for greater than 20 minutes. Patients who had a chest compression fraction of > 0.81 were more likely to achieve ROSC (40% vs 18%, P = 0.004), survive to hospital discharge (20% vs 8%, P = 0.03), and have a favourable neurological outcome (20% vs 7%, P = 0.02).

- The ROC PRIMED study was a factorial study looking at the impact of 30 - 60 seconds versus 3 minutes of CPR prior to defibrillation in patients with out-of-hospital VF arrest.[8] It also assessed an impedance threshold device compared with a sham device. The target recruitment was 13,239 patients; the trial was terminated early for futility after recruitment of 9,933 patients. Survival to hospital discharge with a favourable neurological outcome was 5.9% in both groups.

- The effect of CPR pauses on outcomes was evaluated using further data from the ROC PRIMED study.[9] 2,006 patients were included in the analysis. Survival to hospital discharge was significantly greater in patients with pre-shock pause < 10 s (OR, 1.52; 95% CI, 1.09 to 2.11) compared to those with a pre-shock pause of ≥ 20 s. Similarly, a total peri-shock pause time of < 20 s was associated with higher survival to hospital discharge (OR, 1.82; 95% CI, 1.17 to 2.85) than patients with a peri-shock pause ≥ 40 s.

- The non-inferiority CIRC trial compared manual CPR with an integrated automated load distributing band CPR (iA-CPR) device in 4,231 patients with OOHA.[2] The chest compression fraction was similar in both groups; 80.4% for iA-CPR compared to 80.2% for manual CPR. Survival to hospital discharge was 9.4% in the iA-CPR group and 11.0% in the manual CPR group (adjusted odds ratio 1.06; 95% CI 0.83 to 1.37).

- The PARAMEDIC trial was a cluster randomised trial comparing outcomes following OOHA in 4,471 patients treated with either manual CPR or the mechanical CPR device, LUCAS-2.[3] Only 60% of those in the cluster randomised to receive mechanical CPR device were actually treated with the LUCAS-2 device. There was no difference in 30 day survival; 6% in the mechanical CPR cluster and 7% in the manual CPR cluster (adjusted OR, 0·86; 95% CI, 0·64 to 1·15). Survival with favourable neurological outcome was lower in the mechanical CPR cluster.

- The LINC trial compared manual CPR following the European Resuscitation Guidelines with mechanical CPR using the LUCAS device combined with defibrillation during CPR in 3 minute cycles.[4] 2,589 patients with OOHA were enrolled. There was no difference in the primary outcome measure of four-hour survival (23.6% with mechanical CPR and 23.7% with manual CPR). Survival to hospital discharge with a favourable neurological outcome was similar; 8.3% vs 7.8% in the mechanical and manual CPR groups, respectively.

- Kilgannon and colleagues completed a retrospective study examining the impact of arterial oxygen levels on admission to ICU in post cardiac arrest patients.[7] Hyperoxia was defined as a PaO_2 > 300 mmHg, normoxia as a PaO_2 of 60 to 300 mmHg and hypoxia as a PaO_2 of < 60 mmHg. 6,326 patients were included in the analysis. The following mortality rates were seen: hyperoxia group 63%, normoxia group 45%, and hypoxia group 57%. In comparison to the normoxia group, hyperoxia was associated with a higher risk of death (OR, 1.8; 95% CI, 1.5 to 2.2).

- The TTM trial compared temperature management at 33°C with temperature management at 36°C in 950 patients having suffered an OOHA.[6] There was no difference in mortality between the two groups; 50% in the 33 °C group compared to 48% in the 36 °C group (HR with a temperature of 33°C, 1.06; 95% CI, 0.89 to 1.28; P = 0.51). There was no difference in the rates of favourable neurological outcome. This trial was notable for the low rates of survivors with poor neurological outcomes.

Should we implement this into our practice?
No. There is no benefit from continuous chest compressions during CPR.

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Ringh - Mobile-Phone Dispatch of Laypersons for CPR in Out-of-Hospital Cardiac Arrest

Ringh M, Rosenqvist M, Hollenberg J, Jonsson M, Fredman D, Nordberg P, et al. Mobile-Phone Dispatch of Laypersons for CPR in Out-of-Hospital Cardiac Arrest. New England Journal of Medicine. 2015 Jun 11;372(24):2316–25.

Study synopsis

There is an association between bystander CPR and improved survival in out-of-hospital cardiac arrest (OOHA).[1] This study hypothesised mobile phone positioning systems could be used to dispatch volunteers, trained in CPR, to cases of suspected cardiac arrest and increase rates of bystander CPR. This was a blinded, randomised controlled trial conducted in Stockholm County between April 2012 and December 2013. One dispatch centre covered the whole population. In cases of suspected cardiac arrest, an emergency medical service (EMS) ambulance was dispatched. In addition, fire and police services were dispatched who could act as "first responders".

Lay volunteers, trained in CPR, were recruited by advertising campaign. In cases of suspected OOHA, the dispatch centre activated mobile phone positioning software. Cases were then randomised on a 1:1 basis to receive the intervention or not. In the treatment group, the intervention consisted of lay volunteers within a 500m radius of the OOHA receiving a telephone call, a text message with information on the patient's location and a link to a map showing the patients location. The software was active between 6am and 11pm. In cases randomised to the control group, lay volunteers were located but not contacted in any way. The dispatcher was blinded as to the treatment allocation, as were the investigators.

The exclusion criteria included age less than 8 years; a hazardous environment; OOHA due to drowning, trauma, intoxication, or suicide; and OOHA witnessed by EMS personnel. Using an intention-to-treat analysis, OOHAs where no lay volunteer could be located within 500m were still included in the analysis. The power calculations were based on a pilot study and assumed an increase in bystander initiated CPR from 50% to 62.5%. Thus, 492 patients were needed to achieve 80% power at a two-sided significance level of 5%.

The primary outcome measure was rate of bystander-*initiated* CPR prior to the arrival of EMS or "first responders". Cases where CPR was performed, but only following telephone instructions, were not considered bystander-*initiated* CPR, though this was considered in the secondary analysis. Secondary outcomes included rates of shockable rhythms, rates of return of spontaneous circulation (ROSC), and 30-day survival. Data was sourced from the Swedish Cardiac Arrest Registry, ambulance and first responder records and volunteer surveys.

At the beginning of the study, 5,989 lay volunteers trained in CPR were recruited; by the end of the study, that number had risen to 9,828. One thousand, eight hundred and eight patients underwent randomisation, 794 (43.9%) of these were not in cardiac arrest. A further 347 of these were excluded, mainly as they were not treated by EMS. Ultimately, 306 patients were randomised to the treatment group and 361 to the control group. There were no differences at baseline between the two groups. In 81% of cases, at least one responder was within 500m of the patient in OOHA; in 65% they responded to the alerts; in 23% they were on the scene before first responders or EMS; and in 13% of cases (n =40) they started CPR.

The rates of bystander-initiated CPR was higher in the treatment group; 61.6% versus 47.8% (difference 13.9%; 95% CI, 6.2 to 21.2, P < 0.001). The adjusted odds ratio for likelihood of CPR was 1.7 (95% CI, 1.2 to 2.5) for the treatment group. An additional 8 patients in the treatment group and 25 patients in the control group received telephone instruction CPR. Even with these included, the rates of total bystander CPR was higher in the treatment group (P = 0.01). Regarding the secondary outcomes; there was no difference in: 30-day survival, 11.2% in the treatment group and 8.6% in the control group (P = 0.28); incidence of ROSC, 29.4% and 29.1%, respectively (P = 0.93); and rates of shockable rhythm, 19.3% and 17.3%, respectively (P = 0.52).

Critique

This study demonstrates the use of a mobile phone dispatch system can increase the rate of bystander-initiated CPR. It was carried out in Sweden, where approximately three million of the 9.7 million citizens have been trained in CPR over the last 30 years.[1] This has the potential to provide a crucial link in the chain of survival, along with other initiatives to improve pre-hospital resuscitation.[2,3] The effect this could have if implemented on a population basis is unclear.

The use of bystander CPR initiatives has been the subject of several national initiatives over the past decade in Denmark. These included: mandatory resuscitation training in schools, distribution of CPR self-instruction kits, the placement of 15,000 automated external defibrillators outside hospitals, and improvements in telephone-instruction CPR. These initiatives were associated with an increase in bystander CPR from 21.1% in 2001 to 44.9% in 2010.[2] Over the same period there was an increase in 30-day survival from 3.5% to 10.8%. However, there were a number of alterations to resuscitation guidelines and improvements in post arrest care during this same time period.[2,4,5]

The actual number of patients who benefited from this initiative was low. In 26% of eligible cases, the dispatch system was not activated. There were 9,828 volunteers, yet only 40 patients of the 306 in the treatment group received bystander-initiated CPR. Despite this being a self selecting group, only 57% of the responders who arrived before EMS actually carried out CPR.

The mobile-phone dispatch software was only active between 6am and 11pm; 219 cases of OOHA were not included as they fell outside this time period. The impact of 24 hour-a-day implementation is unclear. Cardiac arrests are twice as common between the daytime hours of 07:00 to 18:59 than at night, 19:00 to 06:59.[6] EMS services must respond to the needs of the whole population, not just OOHA patients, therefore services are concentrated during daytime hours and in urban areas.[6] This results in longer response times in OOHA in rural areas and at night. Mobile-phone dispatch software may be beneficial to those who suffer cardiac arrest at night where access to EMS services are limited.[1] However, it is conceivable volunteers are less willing to be contactable, or inclined to respond, at night, potentially diluting the treatment effect.

This study was carried out in a densely populated city. The effect of implementation on a national basis, encompassing rural populations is, again, unclear. Conceivably the lower population density and greater distances between CPR trained volunteers may delay response times. Analysis of the Swedish Cardiac Arrest Registry demonstrated bystander CPR was associated with a longer EMS response time. It is speculated bystanders feel compelled to act if response times are longer.[1] A prospective observational study has shown the probability of VF decreased with each minute elapsed from time of collapse (OR, 0.92; 95% CI 0.89 to 0.95), whereas the probability of asystole increased (OR, 1.13; 95% CI; 1.09 to 1.18).[7] There is conflicting evidence whether bystander CPR is associated with an increased mortality in those found to be in a non-shockable rhythm.[1,8]

The cost effectiveness of CPR training has been called into question. In a cost analysis, training unselected members of the population in CPR and defibrillation incurred a cost of 202,400 US dollars per quality-adjusted life-year [QALY] gained. This was based on the assumption bystander CPR doubled survival rates.[1,9] If only those who were at high risk of encountering cardiac arrests in the community were trained, the cost fell to 75,000 US dollars per QALY gained.[9] Members of the public who are most likely to encounter an OOHA are those who live with a person over 75 years of age (typically an elderly spouse) or who has cardiac disease. The Swedish Cardiac Arrest Register shows elderly patients who arrest at home are less likely to receive bystander CPR; the proposed reason for this is elderly spouses are less likely to be trained or able to perform CPR.[1] As those who volunteered for this study were a self-selecting group, with an average age of 40, the chance they would encounter an OOHA is low. Of the 9,828 trained volunteers in this study, only 40 commenced bystander CPR prior to the arrival of EMS. In conclusion, it is unclear what effect this initiative would have on patient outcomes if implemented on a national basis and whether it would prove cost effective. A further study, including patient centred outcomes, such as survival, seems warranted.

Where it sits in the body of evidence

- Hasselqvist-Ax and colleagues looked at 22 years of data from the Swedish Cardiac Arrest Register to elucidate the effect of bystander CPR on outcomes.[1] 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 an initial shockable rhythm (41.3% vs 20.7%; P < 0.001), but longer EMS response times (8 min vs 6 min, P < 0.001). After adjustment, the 30-day survival in the group who received bystander CPR remained significantly higher (odds ratio, 2.15; 95% CI, 1.88 to 2.45; P < 0.001).

- Wissenberg and colleagues examined data from Danish Cardiac Arrest Registry from 2001 to 2010, including 19,468 patients with OOHA.[2] 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%) in 2010 (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.[8] 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) after adjustment for arrest confounders.

- Strömsöe and colleagues interrogated the Swedish Cardiac Arrest Register, reviewing all OOHA from 1992 to 2011 (n = 59,926).[10] 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 form 4.8% to 10.7 (P < 0.0001). In 2008 to 2011, of those who achieved ROSC and were hospitalised, 41% were treated with therapeutic hypothermia and 28% underwent percutaneous coronary intervention. Ninety-four of survivors had a favourable neurological outcome (cerebral performance category score of 1 or 2 at discharge).

- A prospective observational study of 873 OOHA patients examined factors influencing the probability VF or asystole. The probability of VF decreased with each minute from time of collapse (OR 0.92, 95% CI 0.89 to 0.95), whereas the probability of asystole increased (OR 1.13; 95% CI, 1.09 to 1.18). Bystander CPR reduced these trends; for VF (OR, 0.97; 95% CI, 0.94 to 0.99) and asystole (OR ,1.09; 95% CI, 1.05 to 1.13).[7]

- A prospective study of bystander defibrillation involving 105 patients demonstrated a delay of less than three minutes from witnessed collapse to defibrillation was associated with a 74% survival.[3] Those who were defibrillated later than three minutes had a 49% survival.

- A cluster randomised controlled trial looked at the impact of continuous CPR compared with CPR interrupted for ventilation in 23,711 cases of OOHA.[11] Survival to hospital discharge was 9.0% in the continuous CPR group compared to 9.7% in the interrupted CPR group (adjusted difference −0.7%; 95% CI, −1.5 to 0.1; P = 0.07). There was no difference in the rates of neurologically favourable outcome.

- The CIRC, PARAMEDIC and LINC trials have compared mechanical CPR with manual CPR in OOHA.[12-14] The LINC trial also included a modified resuscitation algorithm that included defibrillation during a 3 minute period of CPR. All three showed no difference in survival between intervention and control groups.

- Weisfeldt and colleagues performed a prospective analysis of 12,930 OOHA in the USA .[15] 2,042 cardiac arrests occurred in a public place, 9,564 at home, and the remainder in a residential or other private facility. Of those who suffered a cardiac arrest at home, 26% had bystander CPR compared with 45% suffering a cardiac arrest in a public location. The incidence of a shockable rhythm was 22% at home and 51% in a public place. Bystander CPR was associated with a higher likelihood of shockable rhythms (adjusted OR, 1.76; 95% CI, 1.55 to 2.01; P < 0.001). The survival to hospital discharge was 6% for those who arrested at home and 17% for those who arrested in a public location.

Should we implement this into our practice?
No. Further evidence using a patient centred outcome is needed.

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Nakahara – Bystander Interventions in Out-of-Hospital Cardiac Arrest

Nakahara S, Tomio J, Ichikawa M, et al. Association of bystander interventions with neurologically intact survival among patients with bystander-witnessed out-of-hospital cardiac arrest in japan. JAMA. 2015 Jul 21;314(3):247–54.

Study synopsis

This retrospective study used prospectively collected data from the All-Japan Utstein Registry. It examined the association between bystander interventions (bystander CPR and defibrillation) and outcomes following out-of-hospital cardiac arrest (OOHA).

Eligible patients were those who had suffered a bystander witnessed OOHA that was presumed cardiac in origin from January 2005 to December 2012. Patients who had an unwitnessed OOHA or a cardiac arrest witnessed by emergency medical services (EMS) were excluded. The origin of the cardiac arrest (i.e. cardiac or non-cardiac) was determined by physicians after hospital arrival.

In Japan, from 2004 EMS personnel were permitted to use automated external defibrillators (AEDs) without medical instruction (this was previously delivered by telephone or radio). EMS personnel were also permitted to perform endotracheal intubation from July 2004 and to administer adrenaline from April 2006. EMS services are not permitted to cease resuscitation at the scene and must transport the patient to hospital. Public use of AEDs has been permitted from July 2004 and by 2012 an estimated 364,959 AEDs were in place in the community.

The primary outcome measure was neurologically intact survival defined as Glasgow-Pittsburgh cerebral performance category score 1 or 2 or an overall performance category score of 1 or 2 at one month or at discharge, whichever came sooner.

Logistical regression analysis was used to determine the odds ratio for neurologically intact survival associated with bystander CPR and also four categories of defibrillation (none, bystander-only, bystander and EMS combined, and EMS only). Additional analysis was performed to determine the degree of effect these interventions had on outcomes over the eight year study period. Included in the model was calendar year, age, sex, presenting rhythm, interval between EMS call and arrival at scene, interval between arrival at scene and arrival at hospital, adrenaline administration and advanced airway management.

925,288 patients were included in the registry during the eight year study period. 167,912 arrests met the inclusion criteria of bystander witnessed OOHA of presumed

cardiac origin. The incidence of OOHA increased over time from 14.0 per 100,000 persons (95% CI, 13.8 to 14.2) in 2005 to 18.7 per 100,000 persons (95% CI, 18.4 to 18.9) in 2012. The rates of bystander CPR increased from 38.6% to 50.9% during this time period. The rate of bystander defibrillation increased from 0.1% to 2.3%, as did the incidence of patients who had bystander defibrillation followed by EMS defibrillation (0.1% to 1.4%). There was a commensurate decrease in EMS-only defibrillation from 26.6% to 23.5%. The percentage of patients who survived neurologically intact increased from 3.3% (95% CI, 3.0% to 3.5%) to 8.2% (95% CI, 7.8% to 8.6%).

Considering patients who received EMS-only defibrillation as a reference point, the odds ratio for neurologically intact survival was calculated using a logistic regression analysis. Bystander CPR (compared to no bystander CPR) was associated with an increased chance of neurologically intact survival (adjusted OR, 1.52; 95% CI, 1.45 to 1.60). Absence of defibrillation was associated with a lower chance of good neurological survival (adjusted OR, 0.43; 95% CI, 0.39 to 0.48). Bystander-only defibrillation was associated with an increase in neurologically intact survival (adjusted OR, 2.24; 95% CI, 1.93 to 2.61), as was combined defibrillation (adjusted OR, 1.50; 95% CI, 1.31 - 1.71). Overall, 23% of the increase in survival seen between 2005 and 2012 was deemed attributable to increased bystander interventions.

Critique

This is one of a number of Utstein registry-based studies published between 2013 and 2015.[1-3] Like all registry-based studies, there are confounders that cannot be fully accounted for. For example, due to a change in protocol, the use of adrenaline increased from 0.2% to 24.3% during the study period. The authors admit an accurate estimation of the relative risks of adrenaline use and advanced airway management could not be made. Nevertheless, this study provides insight into the impact of bystander defibrillation.

There is a survival benefit for patients who receive bystander CPR or defibrillation.[1-4] A prospective study of bystander defibrillation demonstrated a delay of less than three minutes from collapse to defibrillation was associated with a 74% survival. Those who were defibrillated later than three minutes had a 49% survival.[4] Despite this, the overall benefit to the population as a whole most be weighed up against the cost implications of these measures.

In this study, the associated increase in neurologically intact survival was highest in patients who received bystander-only defibrillation (adjusted OR, 2.24). In this group the survival benefit may be attributable to the return of spontaneous circulation (ROSC) after bystander defibrillation. Comparing those who received both combined bystander and EMS defibrillation with those who had EMS defibrillation only provides a more accurate assessment of the impact of bystander defibrillation (as these patients were

likely to have received bystander defibrillation without ROSC). This combined group had an increased survival (adjusted OR, 1.50) which was almost an identical increase in the survival seen with bystander CPR (adjusted OR, 1.52). In this group, it is unclear whether the defibrillation conferred any survival benefit over and above CPR only. In a study examining the impact of AED use by fire fighters who were first responders, patients who received CPR and defibrillation had a higher survival than those who had CPR only followed by defibrillation after arrival of EMS services (adjusted odds ratio, 1.8; 95% CI, 1.1 to 2.9).[5]

There was a 19 fold increase in bystander defibrillation (bystander-only and bystander combined with EMS) from 46 cases in 2005 to 881 cases in 2012, despite a relatively unchanged rate of shockable rhythms (21.6% to 20.1%). During this time period there was a 33 fold increase in the availability by AEDs. Of the 364,959 AEDs available in 2012, only 881 (0.24%) were used by bystanders that year. AEDs cost from US$1,300 to US$3,000; this does not include the cost of maintenance and training of lay persons in CPR and AED use.[6] In Japan, the fire department train approximately 1.4 million citizens (1% of the population) each year in chest compressions and AED use. CPR training and making AEDs widely available is costly, yet the overall incidence of bystander defibrillation remains low.

The beneficial impact of AEDs depends on the risk profile of the population in the vicinity of the AED, the population density and the density of good Samaritan responders. The investigators argue knowledge of high risk areas for cardiac arrest would maximise AED effectiveness. Alternatively, placement in areas of very high populations density, such as airports and railway terminals would make AEDs beneficial. In 1991, the Australian airline Quantas introduced AEDs at major airports and on all international aircraft. Over a 65 month period, AEDs were used in 46 cardiac arrests (23 patients had a shockable rhythm). During this time period over 200,000 flight segments were flown and 31 million passengers transported.[6] Quality adjusted life years have been used to assess the economic impact of using AEDs to save lives. By placing AEDs on large aircraft, it costs approximately US$35,000 per quality year of life saved. Placing AEDs in large shopping centres or sporting venues costs US$500,000 to US$2 million per quality year of life saved.[6] Despite these costs, an ethical argument is often made for use of AEDs in public areas to encourage bystander interventions. This is not supported by this study; between 2009 and 2012 almost 147,000 were purchased yet the rates of bystander CPR were unchanged; 50.7% in 2009 to 50.9% in 2012. From this paper we can conclude bystander intervention is associated with improved neurologically intact survival following OOHA, but at a significant financial cost.

Where it sits in the body of evidence

- Hasselqvist-Ax and colleagues looked at 22 years of data from the Swedish Cardiac Arrest Register to elucidate the effect of bystander CPR on outcomes.[1] 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 longer EMS response times (8 min vs 6 min, P < 0.001). After adjustment, the 30-day survival in the group who received bystander CPR remained significantly higher (odds ratio, 2.15; 95% CI, 1.88 to 2.45; P < 0.001).

- Wissenberg and colleagues examined data from Danish Cardiac Arrest Registry from 2001 to 2010, including 19,468 patients with OOHA.[2] 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%) in 2010 (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).

- A prospective observational study of 873 OOHA patients examined factors influencing the probability VF or asystole.[7] The probability of VF decreased with each minute from time of collapse (OR, 0.92; 95% CI, 0.89 - 0.95), whereas the probability of asystole increased (OR, 1.13; 95% CI, 1.09 - 1.18). Bystander CPR reduced these trends significantly; for VF (OR, 0.97; 95% CI, 0.94 - 0.99) and asystole (OR, 1.09; 95% CI 1.05 - 1.13).

- A registry-based study from the Scottish Ambulance Service evaluated the impact of EMS response times on outcomes following 14,967 OOHA that were not witnessed by EMS personnel.[8] After adjustment, response times remained a significant predictor of survival. Using logistical regression analysis, a model was derived to predict the survival benefit if response times were less than 5 minutes. This model predicted an increase in survival from 6.2% to 10.5%.

- The impact of mobile phone dispatch systems on rates of bystander CPR was assessed in a randomised controlled trial involving 667 cases of OOHA.[9] Bystander-initiated CPR rates were higher in the group randomised to receive lay responders dispatched by telephone; 61.6% compared with 47.8% in the control group (difference 13.9%; 95% CI, 6.2 to 21.2; P < 0.001). The intervention group had an adjusted odds ratio for likelihood of bystander CPR of 1.7 (95% CI, 1.2 to 2.5). There was no difference in rates of shockable rhythm, ROSC or 30 day survival.

- In a cost analysis, training unselected members of the population in CPR and defibrillation incurred a cost of US$202,400 per QALY gained.[10] This was based on the assumption bystander CPR doubled survival rates. If only those who were at high risk of encountering cardiac arrests were trained, the cost fell to US$75,000 US per QALY gained.

- A meta-analysis involving 33,124 patents examined the impact of defibrillation times on OOHA outcomes.[11] For patients who were defibrillated within 6 minutes of collapse, there was no increased survival with a decreased time to defibrillation. For patients defibrillated between 6 and 11 minutes, there was a linear decrease in survival (OR for survival 0.72; 95% CI, 0.61 to 0.84 for each minute delay to defibrillation). Beyond 11 minutes, there was no further reduction in survival.

- Caffrey and colleagues completed a prospective study examining the use of AEDs stationed 60 to 90 seconds walk apart in three major American airports serving over 100 million passengers per year.[12] There were 21 cases of OOHA. Eighteen patients had a shockable rhythm, 11 of whom were successfully resuscitated. Ten were neurologically intact at one year.

- In a study by White and colleagues examining OOHA due to ventricular fibrillation, 52% of initial defibrillations were carried out by police and fire services equipped with AEDs.[13] The rates of ROSC with defibrillation only was 35% in the group of patients treated by police and fire services compared to 26% in those treated by EMS personnel. There was no statistical difference in survival between patients treated by police and fire service first responders (43%) and those treated by EMS personnel (40%).

Should we implement this into our practice?
Maybe. Bystander interventions improve outcomes in OOHA, but are associated with a significant economic cost.

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Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial. Journal of Hepatology. 2016 Jan 1;64(1):69–78.

Study synopsis

High volume plasma exchange (HVP) in acute liver failure (ALF) is thought to remove plasma cytokines and adhesion molecules and modulate the immune response, limiting progression to multi-organ failure, cerebral oedema and death. This prospective, multi-centre, randomised, controlled trial compared standard medical therapy (SMT) with SMT plus HVP in patients with ALF. The investigators hypothesised HVP would reduce mortality in patients with ALF, and chose transplant free survival as the primary endpoint. A second proof-of-principle study was also carried out, examining the effects of HVP on circulating interleukins, tumour necrosis factor-α, angiopoeitin-2, lymphocytes, and natural killer cells. Please note, the paper appears to contain typographical errors in some sections and results are presented as they are in the paper.

In study A, patients with ALF were randomised to SMT (control group) or SMT plus HVP (hereafter referred to as the HVP group). In study B, 20 patients in the HVP group had their plasma sampled before and after the first dose of HVP. This was compared with 11 controls. The results of study B will not be discussed further in this review.

Patients aged 18 years or older with ALF of any aetiology and grade 2 encephalopathy or worse were eligible. Patients already on the liver transplant list were also considered eligible. The exclusion criteria included chronic liver disease, alcoholic hepatitis, previous liver transplant or moribund state. Patients were recruited within 24 hours of development of grade 2 encephalopathy.

Some aspects of care were protocolised. The target MAP was 60 mmHg, noradrenaline was the first choice vasopressor, dobutamine was the first choice inotrope, the use of other inotropic and vasopressor agents were at the discretion of the treating team. N-Acetylcysteine (NAC) was given to all patients. The dose of HVP was 15% of ideal body weight per session at a plasma removal rate of 1-2 L/h, with fresh frozen plasma (FFP) used as the replacement fluid. HVP was delivered on 3 consecutive days.

Using previous observational data and assuming a 20% reduction in survival, it was calculated 182 patients would be required to give a power of 80% and a significance level of 5%. The primary endpoint was transplant free survival before hospital discharge. Patients who received transplant were censored.

183 patients were recruited from three centres between 1998 and 2010. One patient in

the HVP group withdrew consent leaving 90 patients in the control group and 92 patients in the HVP group. The baseline characteristics of the two groups were well balanced. The majority of patients (134/182) had hyperacute liver failure. One hundred and eight of the 182 cases were due to paracetamol-induced liver failure.

The mean number of HVP sessions was 2.4 ± 0.8 per patient. The average plasma exchange ranged from 9.0 to 9.3 L per treatment resulting in a mean administered dose of 0.33 ± 0.12 L/kg per treatment. Fifty per cent of patients in the HVP group and 49% of patients in the SMT group were listed for liver transplant, with 26.1% and 35.6% undergoing liver transplant respectively (P = 0.17).

Overall survival to hospital discharge was 58.7% of the HVP group and 47.8% of the control group. Following stratification for liver transplantation the hazard ratio for survival to hospital discharge was 0.56 (95% CI, 0.36 to 0.86; P = 0.0083). Of the 56 patients who had a liver transplant, 24 received HVP. HVP did not improve survival in patients who went on to receive liver transplant (P = 0.75). In patients who were deemed not suitable transplant candidates, HVP significantly improved survival (P = 0.03). Despite similar baseline creatinine levels, the HVP group were less likely to require renal replacement therapy (OR, 0.42; 95% CI, 0.23 to 076; P < 0.0045). Patients treated with HVP had a statistically significant improvement in MAP and a commensurate reduction in vasopressor requirement.

Critique

This is the first randomised controlled trial examining the use of high volume plasma exchange in acute liver failure. The proposed mechanism of action of this therapy is removal of toxic metabolites, such as pro inflammatory cytokines and damage-associated molecular patterns (DAMPs), which induce a systemic inflammatory response. This was demonstrated by the proof-of-principle aspect of this study (see original article for further details). In addition, the use of FFP may replenish potentially beneficial coagulation factors, while plasma exchange may have an immunomodulatory effect. This reduction in inflammatory cytokines was associated with a higher MAP, lower vasopressor requirement and lower need for renal dialysis in the HVP group.

This is the first positive trial in this area and, clearly, further work needs to be done. However, HVP has the potential to be of huge importance in ALF for a number of reasons. Firstly, it is the first positive trial on extracorporeal liver support; succeeding where others such as molecular absorbent recirculating system (MARS), Prometheus, single pass albumin dialysis (SPAD) and the hepatocyte based therapies (extracorporeal liver assist device and the HepatAssist System) have failed. Secondly, it can be administered in a non-liver centre without the need for specialised equipment. Thirdly, it benefits those who are not deemed suitable liver transplant candidates.

There are a number of points that warrant discussion in this trial. ALF is a rare condition, affecting between one and six people per million every year.[1] The recruitment process was slow with the trial taking place over 13 years. The lack of a CONSORT diagram means the reader does not know how many patients were screened in this time. The authors state there was no statistically significant difference in outcomes when those recruited in the first and second halves of the study were compared. However, review of the Kaplan-Meier curves in the supplementary material shows that in the control group survival was approximately 25% in the first half of the study compared to 45% in the second half. Although this was not statistically significant, it may indicate an improvement in standard medical treatment during this time. Evidence suggests that the outcomes for patients with ALF undergoing transplantation have also improved steadily over the past two decades.[2] There was no change in the survival for those treated with HVP. It may be that the medical management of ALF has improved with time. Improvements in standard care of sepsis patients have rendered early goal directed therapy redundant.[3,4] This raises the question would HVP show a survival benefit in comparison to standard care in 2016?

The total number of patients was small (n = 183), therefore further work should be done before this is considered standard care. Nevertheless this represents the second largest study of any extracorporeal liver support device. Although this was a multi-centre trial, the vast majority (143/182) of patients came from one centre in Copenhagen. For example, Kings College London recruited just 25 patients over the 13 year study period. During this time between 780 and 4,680 cases of ALF would have been expected in the UK, though only a small proportion of these would have been managed in Kings College.[1] While there was no statistically significant difference in the outcomes for the Copenhagen and non-Copenhagen groups, the numbers in the non-Copenhagen group was small, making it difficult to detect differences in mortality.

Patients who did not receive liver transplantation derived the greatest benefit from HVP. It could be argued this therapy could be delivered in a non-liver centre, especially when patients are deemed not suitable for transplantation. However, all patients in this study were treated in a tertiary referral liver unit (with the majority being treated in Copenhagen). It is not clear whether this improvement in survival would be replicated if HVP was instigated in non-liver units.

In conclusion, HVP has the potential to benefit patients with ALF but more studies are needed to provide external validity. Further studies should look at the optimal dosing and timing of HVP, in which patient groups it should be performed and whether administration of HVP is beneficial if performed outside a liver centre.

Where it sits in the body of evidence

- A retrospective analysis of 4,903 patients from the European Liver Transplant Registry database was conducted to look at outcomes following liver transplantation for ALF.[1] ALF accounted for 8% of liver transplants in the UK. The time period covered was 1998 to 2009. Paracetamol overdose accounted for only 11% of transplantations. Patient survival at 1, 5 and 10 years was 74%, 68%, and 63%, respectively. Graft survival at 1, 5 and 10 years was 63%, 57%, and 50% respectively. Five year survival from 2004 to 2009 was 72%, and was higher than any of the previous quinquennia ($P < 0.001$). In a multivariate Cox regression analysis, paracetamol-related ALF was associated with a higher risk of death or graft loss (RR, 1.24; 95% CI, 1.03 to 1.51, $P = 0.027$).

- In a prospective, double-blind trial, NAC administered for 72 hours was compared to placebo in 173 patients with non-paracetamol induced ALF.[5] There were some imbalances between the groups at baseline, with the placebo group having more females ($P = 0.004$) and a longer duration from jaundice to coma ($P = 0.026$). There was no difference in the primary outcome measure of 3 week survival; 70% for patients given NAC compared with 66% for patients given placebo ($P = 0.283$). There was improved transplant free survival at 3 weeks seen with NAC (40%) compared to those given placebo (27%) ($P = 0.043$). Mixed effects were seen in patients treated with NAC. There was a trend towards improved survival and transplant free survival in patients with grade I-II encephalopathy. However, there was a trend towards poorer survival and transplant free survival in those with grade III-IV encephalopathy.

- The Helios study group looked at the role of the Prometheus machine (an extracorporeal liver support device that works by fractionated plasma separation and adsorption (FPSA)) in acute on chronic liver failure.[6] 145 patients were randomised to standard medical care (SMT) or standard medical care plus at least 8 sessions of FPSA. There was no difference in 28 day survival (66% in the FPSA group versus 63% in the SMT group ($P = 0.70$)) or 90 day survival (47% in the FPSA group versus 38% in the SMT group ($P = 0.35$)).

- The FUMAR study looked at albumin dialysis with the Molecular Adsorbent Recirculating System (MARS) in 102 patients with ALF.[7] Patients were randomised to SMT or SMT plus MARS. There was no difference in the 6 month survival using a modified intention-to-treat analysis; 75.5% in the SMT group compared to 82.9% in the SMT plus MARS group ($P = 0.50$). The high rate of transplantation (66/102) and short delay to transplantation (16.2 hours) may have limited the potential benefit of this therapy.

- Karvellas and colleagues published a small case control study of single pass albumin dialysis (SPAD) involving 6 SPAD treated patients and 7 controls, all with paracetamol induced ALF.[8] SPAD uses a standard renal dialysis circuit and a high flux albumin

permeable haemofilter. The patient is dialysed against an albumin containing dialysate with the dialysate discarded after a single pass. Eleven of the 13 patients met King's College London criteria for transplantation. There was no difference in physiological parameters, biochemistry or survival in ICU or at one year.

- A pilot study of the Extracorporeal Liver Assist Device (ELAD) was carried out involving 24 patients with ALF.[9] Seven patients were already listed for transplantation. 25% of ELAD treated patients had a deterioration in their encephalopathy grade compared to 58% of controls. There was no difference in mortality.

- The HepatAssist liver support system (a porcine hepatocyte based extracorporeal liver support) was evaluated in a prospective, randomised, multicentre, controlled trial involving 171 patients with ALF.[10] There was no difference in 30 day mortality; 71% in the treatment group compared to 62% in the control group (P = 0.26). After adjustment for the effect of liver transplantation, the risk of 30 day mortality remained non-significant.

Should we implement this into our practice?
Maybe, but it is difficult to recommend widespread implementation on the basis of one positive trial.

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Guidelines of Note

There have been a number of excellent, open access critical care guidelines published in 2015. We had started to summarise these, but it was difficult to do without simply rewriting the entire guideline. Instead, these guidelines are listed over the next several pages, as well as on the meeting webpage (www.bit.do/CCR16), including links to the publisher's free accessible paper. Some guidelines are available from the relevant society rather than publisher.

- Part 1: Executive Summary: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S315-S367
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- Part 2: Evidence Evaluation and Management of Conflicts of Interest: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S368-S382
- Part 3: Ethical Issues: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S383-S396
- Part 4: Systems of Care and Continuous Quality Improvement: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S397-S413
- Part 5: Adult Basic Life Support and Cardiopulmonary Resuscitation Quality: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S414-S435
- Part 6: Alternative Techniques and Ancillary Devices for Cardiopulmonary Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S436-S443
- Part 7: Adult Advanced Cardiovascular Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S444-S464
- Part 8: Post–Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S465-S482
- Part 9: Acute Coronary Syndromes: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S483-S500
- Part 10: Special Circumstances of Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S501-S518
- Part 11: Pediatric Basic Life Support and Cardiopulmonary Resuscitation Quality: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S519-S525
- Part 12: Pediatric Advanced Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care.

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The ARCTIC SUN® 5000 Temperature Management System is a surface cooling system that provides clinicians with the ability to initiate patient temperature management in minutes via a programmable, non-invasive method of automated and effective treatment.

ARCTIC SUN® 5000 Temperature Management System – Setting a new standard for performance, safety and simplicity.

Arctic Sun and Bard are registered trademarks of C.R. Bard Inc., or an affiliate.

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Cook Medical

A global pioneer in medical breakthroughs, Cook Medical is committed to creating effective solutions that benefit millions of patients worldwide. Today, we combine medical devices, drugs, biologic grafts and cell therapies across more than 16,000 products serving more than 40 medical specialties. Founded in 1963 by a visionary who put patient needs and ethical business practices first, Cook is a family-owned company that has created more than 10,000 jobs worldwide.

Cook manufactures the Cook Staged Extubation Set, Turbo Flo Acute Haemodialysis Catheter, Ciaglia Blue Rhino G2 Advanced Percutaneous Tracheostemy Introducer Set, Central Venous Access Devices, Blocker Sets, and Tiger 2 Self Advancing Nasal Jejunal Feeding Tube.

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Fannin

At Fannin we provide the medical devices, medicines and diagnostic products that help healthcare professionals and patients across the Island of Ireland and the UK manage illness and restore health. But what we deliver is more than simply the mechanics of treatment. We seek to be the best service provider of Medical Devices, Medicines and Services to the healthcare sector.

Our portfolio covers Anaesthesia, Critical Care, Surgical and we represent some of the most respected manufacturers in the world including Fujifilm Sonosite Ultrasound, Fresenius Kabi infusion technology, Bowa Medical electrosurgery, Airtraq Video guided intubation and Portex Anaesthesia needles amongst many others.

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Fisher Paykel Healthcare

Fisher and Paykel Healthcare are a leading designer and manufacturer of innovative healthcare devices which incorporate unique features to improve patient care.

Our Critical Care team would like to demonstrate Optiflow™. Optiflow™ is a revolutionary respiratory support system which offers the ability to comfortably deliver a complete range of oxygen concentrations and flows to extend the traditional boundaries of oxygen therapy.

This is achieved through the integration of heated humidification and a precise blend of air and oxygen delivered via an innovative nasal cannula. Clinical data suggests that Optiflow may lead to:

- More effective treatment and reduced escalation of care
- Increased patient and caregiver satisfaction
- Reduced length of stay in ICU
- Reduced cost of care

THRIVE using Optiflow™ is changing the way emergency and difficult intubations are managed - from a pressured start-stop process to a smooth and unhurried undertaking. Optiflow™ increases apnoea time in difficult airway patients undergoing general anaesthesia which makes securing a definitive airway a smooth and unpressured undertaking.

Come along to our stand and try it yourself.

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Norso Medical

Norso Medical Limited, A local supplier of medical equipment ranging from Patient Monitors, Ultrasound and Pre Hospital Monitoring strive to bring state of the art products to areas such as Anesthetics, ICU, General Wards and Pre-Hospital Transport.

Recently accredited with ISO 9001:2008, Norso Medical Limited understand the needs of clinical and technical clients and supply a high standard of sales, service and aftersales care with our dedicated clinical trainers, highly knowledgeable technical staff and customer services team.

Norso Medical Limited is the sole exclusive sales/service agent for Mindray Patient Monitors and Ultrasound, Masimo Co Oximetry and RDT pre hospital transport in Ireland. These products are innovative and world leading in their class.

Masimo Co Oximetry is leading the way in non-invasive monitoring with their rainbow technology including their total hemoglobin for spot check and long term monitoring. Masimo have also recently released 4 channel EEG and cerebral Oximetry '03'.

Norso Medical has attained a large market share and won multiple framework competitions making Mindray Patient Monitoring one of the leaders in its class in all areas of acute and general wards. These range of monitors truly meet the needs of patients in all areas of care.

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Orion Pharma

Orion is a Finnish born innovative European R&D based pharmaceuticals and diagnostics company with an emphasis on developing medicinal treatments and diagnostic tests for global markets. Orion develops, manufactures and markets human and veterinary pharmaceuticals and active pharmaceutical ingredients as well as diagnostic tests.

Orion carries out extensive research with a goal of introducing new treatments into global markets. The core therapy areas in Orion's product and research strategy are central nervous system, oncology, critical care and respiratory medicines.

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Pfizer

At Pfizer, we apply science and our global resources to improve health and well-being at every stage of life. We strive to set the standard for quality, safety and value in the discovery, development and manufacturing of medicines. Our diversified global health care portfolio includes biologic and small molecule medicines and vaccines, as well as many of the world's best-known consumer products.

Every day, Pfizer colleagues work to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as the world's leading biopharmaceutical company, we also collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, Pfizer has worked to make a difference for all who rely on us. In the UK, Pfizer has its business headquarters in Surrey and is a major supplier of medicines to the NHS. To learn more about our commitments, please visit us at www.pfizer.co.uk.

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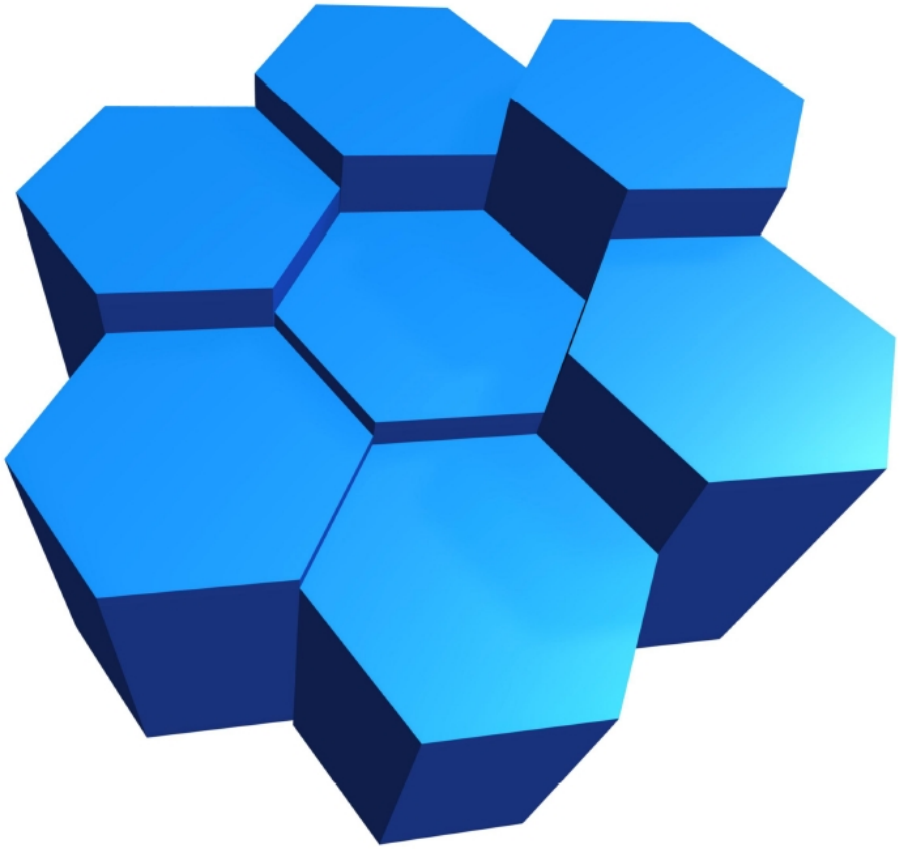

NIICS

Critical Care Reviews Meeting 2017

Titanic Centre, Belfast

Friday January 27th