The results of some highly anticipated clinical trials and studies will be presented on 21 March 2017 at the opening ceremony of the 37th ISICEM in Brussels.

The opening session will take place from 08.30-10.00 and will surely present some fascinating interpretations and conclusions, so mark your calendar to ensure you don’t miss it.

The following studies are among those to be presented:

**Meta-analysis of 3 Trials Comparing Protocolised With Usual Resuscitation in Patients Presenting to the ED With Severe Sepsis and Septic Shock**

The publication in 2001 by Rivers and colleagues of a single-centre, randomised clinical trial (RCT) of early goal-directed therapy (EGDT) versus usual care for patients with septic shock was very influential and profoundly affected the Surviving Sepsis Campaign guidelines. Subsequently, three multicentre RCTs failed to demonstrate a reduction in mortality for EGDT over usual care (ProCESS, ProMISe and ARISE).

Prof. Rinaldo Bellomo, Australian and New Zealand Intensive Care Research Centre, explained to ICU Management & Practice that as there is considerable variability among patients who develop septic shock, consequently, important treatment effects in patient subgroups or particular settings may have been missed. In contrast, a prospective individual patient data meta-analysis provides greater statistical power to identify subgroup effects. The goals of the PRISM study were to use individual data from the three trials to determine the effect of EGDT versus usual care on several key outcomes and to compare the effects of EGDT across specific patient and care delivery subgroups.

The results of the individual patient analysis of data will be presented by Prof. Bellomo. The study is due to be published in the New England Journal of Medicine.

**Effects of a National Norepinephrine Shortage on Patients with**

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Dr. Hannah Wunsch, will be presenting on this study, to be published in JAMA. This study assessed the association between the national shortage of norepinephrine that occurred in the US in 2011 and hospital mortality rates among patients with septic shock.

Dr. Wunsch explained to ICU Management & Practice that this study took advantage of a natural experiment. In 2011 there was a national shortage of norepinephrine in the U.S. This shortage officially lasted for twelve months, but had variable impact in different hospitals.

The researchers used data from Premier – an administrative database of approximately 20% of US hospital admissions, which provided information on medications each patient received daily in hospital. The team identified all the patients with septic shock admitted to these hospitals over five years (between July 2008 and July 2013). 26 hospitals showed more than a 20% relative decrease in norepinephrine use during at least 3 months in 2011. Wunsch explained that it is, however, important to note that most hospitals examined were not affected by the shortage (consistent use hospitals n=102).

For patients in the 26 “shortage” hospitals, the rate of norepinephrine use dropped from a baseline rate of 77.0% of patients to a nadir of 55.7% during the shortage period. Results of the study show that the drug shortage had an effect on the use of alternative vasopressors, in particular phenylephrine. Use of phenylephrine in patients with septic shock increased from a baseline rate of 36.2% to a peak of 54.5% in 2011, and then dropped back down again.

In these “shortage” hospitals, the hospital mortality rate for patients admitted during a period of shortage was 39.6% versus 35.9% at other times, with an adjusted odds ratio for mortality of 1.15 (95% CI 1.01-1.30; P=0.03). Because mortality rates can change over time, researchers also did a difference-in-difference analysis, which compared mortality changes over time in shortage hospitals with the consistent-use hospitals and found the same result.

This study has a number of important findings, emphasises Wunsch. At the policy level, this study is important for demonstrating that a shortage of a medication can lead to substantial changes in care delivery and, in the case of norepinephrine, may have contributed to hundreds of excess deaths. Also, for critical care practitioners, these data raise questions regarding the best choice of vasopressor for patients in septic shock. The study is unique for allowing us to detect mortality differences that would be almost impossible in a randomised controlled trial of vasopressors due to the enormous sample size required. It is important to note that we cannot determine whether the increased mortality rate was due to the specific choice of phenylephrine as a substitute, or whether any alternative to norepinephrine might be associated with worse outcomes.

Lung Recruitment in ARDS Randomised Controlled Trial

The objective of this trial by Prof. Marcelo B.P. Amato, University of São Paulo, Brazil and colleagues, was to test whether an intensive alveolar-recruitment strategy could further reduce postoperative pulmonary complications, when added to a protective ventilation with small-VT.

**Background:** Perioperative lung-protective ventilation has been recommended to reduce pulmonary complications after cardiac surgery. The protective role of a reduced tidal-volume (VT) has been established within this scenario, whereas the added-protection afforded by alveolar-recruiting strategies remains controversial.

**Study methods and outcome:** In a prospective, controlled trial, the team randomly assigned 320 high-risk adults presenting hypoxia after cardiac surgery (P/F ratio < 250) to receive either an intensive alveolar-recruitment strategy (Intensive-RS) or a moderate alveolar-recruitment strategy (Moderate-RS), in addition to protective ventilation with small-VT.

For the first time since the publication of the original trials on lung protection (years 1998-2000), an alveolar recruiting strategy appears to present a beneficial impact on hard outcomes, decreasing the occurrence of pulmonary complications, the need for supplemental oxygen and the use of noninvasive ventilation in the
following days, resulting in a shorter hospital stay.

Many secondary physiological outcomes supported the consistency of the main outcome and the long lasting benefits on lung function. Of note, the tested strategy did not increase utilisation of hospital resources.

The results are due to be published in *JAMA*.

## Inotropic Support After Cardiac Surgery

The results of the Levosimendan in High Risk Patients Undergoing Cardiac Surgery (CHEETAH) study will be presented by Prof. Giovanni Landoni, Vita-Salute San Raffaele University, Milan, Italy.

This was a multicentre, randomised, double-blind, placebo-controlled study to investigate whether levosimendan could reduce mortality in cardiac surgery patients requiring perioperative hemodynamic support.

**Background:** Acute perioperative ventricular dysfunction is a major complication affecting up to 20% of patients undergoing cardiac surgery and is associated with increased mortality. Inotropic drugs are the cornerstone of therapy. However, no randomised controlled trials have demonstrated the superiority of any inotropic agent in terms of major clinical outcomes. Furthermore, meta-analyses and observational studies suggest that catecholamines and phosphodiesterase-3 (PDE-3) inhibitors may increase mortality. In contrast, levosimendan is the only inotropic agent associated with improved survival in meta-analyses, especially those involving cardiac surgery patients. Compared with catecholamines and PDE-3 inhibitors, levosimendan increases cardiac output with minimal effect on myocardial oxygen consumption. In addition, it has anti-oxidant, anti-inflammatory, and direct cardioprotective effects.

**Study methods and outcomes:** The study enrolled 506 patients from 14 hospitals spread across three countries. Patients were randomised to receive levosimendan (continuous infusion at a dose of 0.025-0.2 µg/kg/min) or placebo, for up to 48 hours or until intensive care unit (ICU) discharge, in addition to standard care. The primary outcome was 30-day mortality. Secondary endpoints were acute kidney injury, need for renal replacement therapy, a composite endpoint of mortality and need for renal replacement therapy, duration of mechanical ventilation, ICU and hospital length of stay.

The study is due to be published in the *New England Journal of Medicine*.

For a full explanation of the studies, methods used, results and conclusions, we strongly recommend that you attend this popular ISICEM session.

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