

## CONGRESS REPORT

# Major trials presented at the ESICM LIVES in Barcelona, 29 and 30 September 2014

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This year, the ESICM LIVES annual congress hosted many presentations of new trials. So many that not only the traditional 'Hot Topics' session on Wednesday afternoon featured the new papers often synchronously published in *N Engl J Med* and *JAMA*. Sessions were also held on the Monday and Tuesday, when new studies were presented to the delegates of the ESICM. This report aims at providing an overview of these presentations.

**Monday, 29 September 2014***Corti-TC trial*

The session was kicked-off by the Corti-TC trial. The study aimed at giving hydrocortisone and fludrocortisone for prevention of hospital-acquired pneumonia in patients with severe traumatic brain injury. Asehnoune has already presented this in *Lancet Respir Med*.<sup>1</sup> The French Corti-TC trial, a double-blind, multicentre phase 3, randomised placebo-controlled trial, tested the efficacy of low-dose (200 mg) hydrocortisone with 50 µg fludrocortisone for the prevention of hospital-acquired pneumonia in patients with traumatic brain injury-induced adrenal insufficiency. Before receiving the study drug, adrenal function was assessed with a short corticotrophin test. Treatment was stopped if patients had no adrenal insufficiency. The primary outcome was the occurrence of hospital-acquired pneumonia within 28 days after randomisation.

The study enrolled 336 patients (168 assigned to each group). Eight patients withdrew consent. At day 28, 74 of 165 patients (45%) in the steroid group and 87 of 163 (53%) in the placebo group had developed one or more episodes of hospital-acquired pneumonia (hazard ratio [HR] 0.75, 95% CI 0.55-1.03,  $p = 0.07$ ). Low-dose hydrocortisone with fludrocortisone did not improve the outcome of patients with traumatic brain injury. The study may have been underpowered because the proportion of patients with hospital-acquired pneumonia in the placebo group was lower than expected.

*Fenoldopam*

The study by Bove et al.<sup>2</sup> was presented by Giovanni Landoni. This Italian multicentre, randomised, double-blind, placebo-controlled, parallel-group study was performed to determine whether fenoldopam reduces the need for renal replacement therapy in critically ill cardiac surgery patients with acute kidney injury.

The study enrolled 667 patients admitted to intensive care units (ICUs) after cardiac surgery with early acute kidney injury ( $\geq 50\%$  increase of serum creatinine level from baseline or oliguria for  $\geq 6$  hours) to receive fenoldopam (338 patients) or placebo (329 patients). The primary endpoint was the rate of renal replacement therapy. Secondary endpoints included mortality (ICU and 30-day mortality) and the rate of hypotension during study drug infusion. The study was stopped for futility as recommended by the safety committee after a planned interim analysis. Sixty-nine of 338 patients (20%) allocated to the fenoldopam group and 60 of 329 patients (18%) allocated to the placebo group received renal replacement therapy ( $p = 0.47$ ). Mortality at 30 days was 78 of 338 (23%) in the fenoldopam group and 74 of 329 (22%) in the placebo group ( $p = 0.86$ ). Hypotension occurred in 85 (26%) patients in the fenoldopam group and in 49 (15%) patients in the placebo group ( $p = 0.001$ ).

Among patients with acute kidney injury after cardiac surgery, fenoldopam infusion, compared with placebo, did not reduce the need for renal replacement therapy or risk of 30-day mortality but was associated with an increased rate of hypotension.

Barney Reeves presented the TITRe2 study (Transfusion Indication Threshold Reduction) on liberal or restricted transfusion therapy after cardiac surgery. This study has not been published yet. This randomised controlled trial (RCT) was performed in 17 cardiac surgery centres in the United Kingdom. Both postoperative anaemia and red cell transfusion are associated with poor outcome. Cochrane analysis slightly

favours restricted transfusion. The study was performed as an open trial, randomised after occurrence of anaemia (Hb < 9.0g/dl) using two thresholds, 9 and 7.5 g/dl.

The primary outcome was a composite endpoint of serious infection or ischaemic events or acute kidney injury. About 1000 patients were enrolled in each group. There was no significant difference in primary composite outcome. Sensitivity analyses and subgroup analyses did not show significant differences. In the secondary outcomes, there was a signal that suggests that more liberal transfusion is beneficial. This may not be unimportant, as the secondary endpoint for which this was the case was mortality.

#### *PARAMEDIC trial*

Gavin Perkins from the United Kingdom presented the not yet published PARAMEDIC trial (Prehospital Randomised Assessment of a Mechanical Compression Device In Cardiac Arrest). The trial is a pragmatic cluster randomised study of the LUCAS-2 device in adult patients with non-traumatic, out-of-hospital cardiac arrest (OHCA). We already have three negative trials in the field of automated chest compressions: the ASPIRE and CIRC trials using the Autopulse and the LINC trial using the LUCAS.

Survival after OHCA is closely linked to the quality of cardiopulmonary resuscitation (CPR), but in real life, resuscitation during prehospital care and ambulance transport is often suboptimal. Mechanical chest compression devices deliver consistent chest compressions, are not prone to fatigue and could potentially overcome some of the limitations of manual chest compression. However, there is no high-quality evidence that they improve clinical outcomes, or that they are cost-effective.

The primary endpoint of the trial was mortality at 30 days post-OHCA, compared with manual chest compression. Secondary objectives of the study were survival to 12 months, cognitive and quality-of-life outcomes and cost-effectiveness. Ambulance service vehicles were randomised to either manual compression (control) or LUCAS arms. The study included 4471 patients, 1652 were randomised to the LUCAS device and the manual CPR group had 2819 patients.

The study showed no difference in 30-day survival: 6.3% in LUCAS vs. 6.9% in manual CPR. Secondary outcome showed a lower good outcome (CPC 1 and 2) in LUCAS arm; 4.7% vs. 6.0%. So we have a fourth negative trial in the field of automated chest compressions.

#### *High-protein enteral nutrition*

Zandrie Hofman presented the study on high-protein enteral nutrition, enriched with immune modulating nutrients (IMHP) vs. standard high protein (HP) enteral feeding.<sup>3</sup> This was an RCT, funded and executed by Nutricia research.

Enteral administration of immune-modulating nutrients (e.g., glutamine, omega-3 fatty acids, selenium, and antioxidants)

has been suggested to reduce infections and improve recovery from critical illness. However, controversy exists on the use of immune-modulating enteral nutrition, reflected by lack of consensus in the guidelines. The RCT included a six-month follow-up period in 14 ICUs in the Netherlands, Germany, France, and Belgium.

A total of 301 adult patients who were expected to be ventilated for more than 72 hours and to require enteral nutrition for more than 72 hours were randomised to the IMHP (n = 152) or HP (n = 149) group and included in an intention-to-treat analysis, performed for the total population as well as predefined medical, surgical, and trauma subpopulations.

There were no statistically significant differences in incidence of new infections between the groups: 53% (95% CI 44%-61%) in the IMHP group vs. 52% (95% CI 44%-61%) in the HP group (p = 0.96). No statistically significant differences were observed in other endpoints, except for a higher six-month mortality rate in the medical subgroup: 54% (95% CI 40%-67%) in the IMHP group vs. 35% (95% CI 22%-49%) in the HP group (p = 0.04), with a hazard ratio of 1.57 (95% CI 1.03-2.39, p = 0.04) for six-month mortality adjusted for age and APACHE II score comparing the groups.

Among adult patients breathing with the aid of mechanical ventilation in the ICU, IMHP compared with HP did not improve infectious complications or other clinical endpoints and may be harmful as suggested by increased adjusted mortality at six months in a subgroup of medical patients. These findings do not support the use of IMHP nutrients in these patients.

#### **Tuesday, September 30, 2014**

##### *Sepsis guidelines*

Current sepsis guidelines recommend antimicrobial treatment within one hour after onset of sepsis-related organ dysfunction and surgical source control within 12 hours.<sup>4</sup> The objective of this study was to explore the association between initial infection management according to sepsis treatment recommendations and patient outcome.

In a prospective observational multicentre cohort study in 44 German ICUs, we studied 1011 patients with severe sepsis or septic shock regarding times to antimicrobial treatment, source control, and adequacy of antimicrobial treatment. Primary outcome was 28-day mortality.

Median time to antimicrobial treatment was 2.1 (IQR 0.8 - 6.0) hours and 3.0 hours (-0.1 - 13.7) to surgical source control. Only 370 (36.6%) patients received antimicrobial treatment within one hour after organ dysfunction in compliance with the recommendations. Among 422 patients receiving surgical or interventional source control, those who received source control later than six hours after onset of organ dysfunction had a significantly higher 28-day mortality than patients with earlier source control (42.9% vs. 26.7%, p < 0.001). Time to antimicrobial treatment was significantly longer in ICU

and hospital non-survivors; no linear relationship was found between time to antimicrobial treatment and 28-day mortality. Regardless of timing, the 28-day mortality rate was lower in patients with adequate than non-adequate antimicrobial treatment (30.3% vs. 40.9%,  $p < 0.001$ ).

A delay in source control beyond six hours may have a major impact on patient mortality. Adequate antimicrobial treatment is associated with improved patient outcome but compliance with guideline recommendations requires improvement. There was only indirect evidence about the impact of timing of antimicrobial treatment on sepsis mortality.

#### *The SPOT (Light) study*

The SPOT (Sepsis Pathophysiological & Organisational Timing) (Light) study is a prospective observational multicentre study of patients deteriorating on the ward.<sup>5</sup> ICUs in the United Kingdom are very often fully occupied. What is the effect of ICU admission on the patient deteriorating on the ward? There were two groups: early vs. delayed ICU admission; the primary outcome was 90-day mortality. Forty-eight hospitals participated, over 20,000 patients were evaluated, 13,000 included, 12,500 analysed, of which 4500 were admitted to the ICU; about 2400 of these admissions were early.

Results: unadjusted mortality was higher with early admission, because these patients were more severely ill. After adjustment, there was also a higher probability of dying if admitted early. There was no relation between occupancy of ICU beds and 90-day mortality or early admission.

#### *High flow nasal cannula oxygen*

High Flow Nasal Cannula oxygen (HFNC), Optiflow, may be better tolerated than non-invasive ventilation (NIV) and 100% oxygen may be given, according to Frat's study,<sup>6</sup> which was conducted in 23 centres in France and one in Belgium. Randomisation was in three groups: standard oxygen, HFNC and NIV. Acute respiratory failure was defined as a respiratory rate of 24/min; a  $P_aO_2/F_iO_2$  ratio  $< 300$  mmHg and a  $P_aCO_2 < 45$  mmHg. Failure in a group was defined as a respiratory rate  $> 40$ /min, acidosis or  $SpO_2 < 90\%$ . Mainly community- and hospital-acquired pneumonia patients were included with a  $P_aO_2/F_iO_2$  ratio of about 150 mmHg. The primary outcome measure was intubation rate. The secondary outcomes were ICU and 90-day mortality, and ventilator-free days.

There were 310 patients included in two years, about 100 per group. According to an intention-to-treat analysis there was no difference between groups. In patients with a  $P_aO_2/F_iO_2$  ratio  $< 200$  mmHg, HFNC resulted in fewer intubations. ICU mortality and 90-day mortality were lower in the HFNC group. Also there were more ventilator-free days in the HFNC group. We might thus consider to use the Optiflow or similar systems and this may reduce mortality in especially the very sick acute respiratory failure patients.

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