

# Recent Literature Review: No clues, EQ, and what does not work

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Would we detract Delirium, a common yet under diagnosed form of organ failure if we knew its implications well? Is intuition, experience also called good sound judgment and Now evidence based medicine? To advance science of medicine from art of medicine we must know what does not work more than what does at times.

## Delirium as a predictor of Mortality in mechanically ventilated patients

This prospective study<sup>1</sup> was conducted to determine if delirium is an independent Predictor of clinical outcomes, including 6-month mortality and length of stay among ICU patients receiving mechanical ventilation. 275 consecutive mechanically ventilated patients admitted to adult medical and coronary ICUs of a US university-based medical center between February 2000 and May 2001 were included in the study. Patients were followed up for development of delirium over 2158 ICU days using the Confusion Assessment Method for the ICU and the Richmond Agitation-Sedation Scale. Primary outcomes included 6-month mortality, overall hospital length of stay, and length of stay in the post-ICU period. Secondary outcomes were ventilator-free days and cognitive impairment at hospital discharge.

Of 275 patients, 51 (18.5%) had persistent coma and died in the hospital. Among the remaining 224 patients, 183 (81.7%) developed delirium at some point during the ICU stay. Baseline demographics including age, co morbidity scores, dementia scores, activities of daily living, severity of illness, and admission diagnoses were similar between those with and without delirium ( $P > 0.05$  for all). Patients who developed delirium had higher 6-

months mortality rates (34% vs. 15%,  $P = 0.03$ ) and spent 10 days longer in the hospital than those who never developed delirium ( $P < 0.001$ ). After adjusting for covariates (including age, severity of illness, co morbid conditions, coma, and use of sedatives or analgesic medications), delirium was independently associated with higher 6-months mortality (adjusted hazard ratio [HR], 3.2; 95% confidence interval [CI], 1.4-7.7;  $P = 0.008$ ), and longer hospital stay (adjusted HR, 2.0; 95% CI, 1.4-3.0;  $P < 0.001$ ). Delirium in the ICU was also independently associated with a longer post-ICU stay (adjusted HR, 1.6; 95% CI, 1.2-2.3;  $P = 0.009$ ), fewer median days alive and without mechanical ventilation (19 [interquartile range, 4-23] vs. 24 [19-26]; adjusted  $P = 0.03$ ), and a higher incidence of cognitive impairment at hospital discharge (adjusted HR, 9.1; 95% CI, 2.3-35.3;  $P = 0.002$ ). More research is warranted to implement effective delirium prevention, management plan.

## Low Molecular Weight Heparin as effective and safe as dose adjusted unfractionated heparin for non-massive PE

Fourteen randomized trials comparing fixed dose subcutaneous low-molecular weight with dose adjusted intravenous unfractionated heparin for the treatment of non massive symptomatic pulmonary embolism or asymptomatic pulmonary embolism in the context of symptomatic deep venous thrombosis were selected in this meta-analysis.<sup>2</sup> Two reviewers independently extracted data related to study design, quality and clinical outcomes including symptomatic venous thromboembolism, death and major and minor bleeding. Odds ratio for individual outcomes were calculated for each trial and were pooled. Compared with unfractionated heparin, low-molecular-weight heparin was associated with a non-statistically significant decrease in recurrent symptomatic venous thromboembolism at the end of treatment (1.4% vs. 2.4%;

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odds ratio, 0.63 [95% CI, 0.33 to 1.18]) and at 3 months (3.0% vs. 4.4%; odds ratio, 0.68 [CI, 0.42 to 1.09]). Similar estimates were obtained for patients who presented with symptomatic pulmonary embolism (1.7% vs. 2.3%; odds ratio, 0.72 [CI, 0.35 to 1.48]) or asymptomatic pulmonary embolism (1.2% vs. 3.2%; odds ratio, 0.53 [CI, 0.15 to 1.88]). For major bleeding complications, the odds ratio favoring low-molecular-weight heparin (1.3% vs. 2.1%; odds ratio, 0.67 [CI, 0.36 to 1.27]) was also not statistically significant.

A large sample randomized study is needed to put the question to rest.

### Evidence-based Medicine for VAP

An elegant study from St Louis, Missouri, evaluated antibiotic discontinuation policy vs. clinical judgment in cases of VAP.<sup>3</sup> This was a prospective, randomized, controlled trial of 290 adults consecutively treated with antibiotics for VAP. Patients were randomized to receive an antibiotic regimen controlled by either a discontinuation policy (discontinuation group,  $n = 150$ ) or the clinical judgment of their treating physician team (conventional group,  $n = 140$ ). It was recommended that all patients with suspected VAP be started on combination IV vancomycin, 1 g every 12 hours, or linezolid, 600 mg every 12 hours (for gram-positive bacterial infection), and the combination of cefepime, 1 g every 12 hours, and either ciprofloxacin, 400 mg every 12 hours, or gentamicin, 5 mg/kg once daily (for gram-negative bacterial infection). Researchers selected the cefepime and ciprofloxacin or cefepime and gentamicin regimen because they provided adequate treatment for > 90% of gram-negative bacterial isolates from patients with VAP on the basis of the medical intensive care unit (ICU)-specific antibiogram. The antibiotics were discontinued per policy if a noninfectious etiology for the infiltrates not requiring antibiotics was identified (i.e., atelectasis), if the signs and symptoms suggesting active infection had resolved or decreased by > 25% from the peak value, if there was an improvement or lack of progression on the chest radiograph, if there was an absence of purulent sputum, and if there was a PaO<sub>2</sub>/FiO<sub>2</sub> ratio > 250. Physicians could override the discontinuation policy at any time in the care of their patients.

The recommended initial antibiotic regimen for VAP was used by 81.3% of the discontinuation group patients and in 83.6% of the conventional group patients ( $P = 0.617$ ).

Treatment with a single recommended antibiotic directed against gram-negative bacteria or failure to treat with a gram-positive antibiotic accounted for variances in using the antibiotic recommendations. The number of patients having noninfectious etiologies for their pulmonary infiltrates identified was 8.7% in the discontinuation group and 6.4% in the conventional group ( $P = 0.472$ ). Overall, the duration of antibiotic therapy was shorter in the discontinuation group ( $6.0 \pm 4.9$  days) when compared with the conventional group ( $8.0 \pm 5.6$  days,  $P = 0.001$ ). Hospital mortality among the discontinuation group was 32.0% ( $n = 48$ ) vs. 37.1% ( $n = 37$ ) in the conventional group ( $P = 0.357$ ), and the ICU length of stay was slightly shorter in the discontinuation group ( $6.8 \pm 6.1$  days) than in the conventional group ( $7.0 \pm 7.3$  days).

### Nitric Oxide Synthase Inhibitor NG-methyl-L-arginine for severe shock

Septic shock is the leading cause of death in intensive care units. Excessive vasodilatation resulting in hypotension is a hallmark of patients with septic shock. Nitric oxide over production has been found to play an important role in the development of vasodilatation during septic shock. NO is continuously produced at low concentrations by a calcium-dependent nitric oxide synthase (cNOS) from L-arginine. The cNOS enzyme is present in the endothelium and is important for the maintenance of normal vascular tone. Increased production of NO has been demonstrated in clinical sepsis and has subsequently been associated with the development of hypotension, decreased responsiveness to vasopressor agents, maldistribution of blood flow, increased microvascular leakage, tissue dysoxia, and multiple organ dysfunctions. Reducing the overproduction of NO by partial inhibition of nitric oxide synthase could therefore be a useful intervention in the treatment of septic shock. This study<sup>4</sup> was conducted to assess the safety and efficacy of the nitric oxide synthase inhibitor 546C88 in patients with septic shock. The predefined primary efficacy objective was resolution of shock, defined as a mean arterial pressure >70 mm Hg in the absence of both conventional vasopressors and study drug, determined at the end of the 72-hr treatment period.

A total of 312 patients with septic shock diagnosed within 24 hr before randomization were allocated to receive either 546C88 or placebo (5% dextrose) by intravenous infusion for up to 72 hrs. Conventional vasoac-

tive therapy was restricted to nor epinephrine, dopamine, and dobutamine. Study drug was initiated at 0.1 mL/kg/hr (5 mg/kg/hr 546C88) and titrated according to response up to a maximum rate of 0.4 mL/kg/hr with the objective to maintain mean arterial pressure at 70 mm Hg while attempting to withdraw any concurrent vasopressors. Requirement for vasopressors, systemic hemodynamics, indices of organ function and safety (including survival up to day 28) were assessed. The median mean arterial pressure for both groups was maintained >70 mm Hg. Administration of 546C88 was associated with a decrease in cardiac index while stroke index was maintained. 40% and 24% of the patients in the 546C88 and placebo cohorts achieved resolution of shock at 72 hrs, respectively ( $P = 0.004$ ). There was no evidence that treatment with 546C88 had any major adverse effect on pulmonary, hepatic, or renal function. Day 28 survival was similar for both groups. The study has demonstrated that intravenous infusion of the NOS inhibitor 546C88 for up to 72 hours titrated in accordance with dosing algorithm intended to maintain MAP of 70 mm Hg can promote the resolution of shock with acute circulatory failure due to severe sepsis. In this study, survival was not a predefined outcome measure but rather it was assessed as a safety measure. However, a large phase-III study was discontinued prematurely due to increased mortality in treatment group.

In March came out a landmark publication<sup>5</sup> from the multinational Surviving Sepsis Campaign after a consensus conference. This document gives evidence-based guidelines for management on severe sepsis and septic shock. A heavily underlined, ragged copy must be found in each nursing station, of an ICU.

### **High-dose Epinephrine causes better outcome in cardiac arrest in children!!!**

This prospective, randomized, double blind trial<sup>6</sup> was performed to compare high-dose epinephrine (0.1 mg per kilogram of body weight) with standard-dose epinephrine (0.01 mg per kilogram) as rescue therapy for in-hospital cardiac arrest in children after failure of an initial, standard dose of epinephrine. The trial included 68 children. The primary outcome measure was survival 24 hours after the arrest. A total of 68 children were enrolled, and survival was lower in the group randomized to receive high-dose epinephrine (adjusted odds ratio for death 7.9). There was no difference between groups

in terms of return of spontaneous circulation. None of the patients in the high-dose group survive the hospital discharge, compared with 4 of those in the standard is group. Among the 30 patients whose cardiac arrest was precipitated by asphyxia, none of the high-dose patients were alive at 24 hours, compared with 39% of those in the standard-dose group.

Cardiac arrest in children is a much different phenomenon, most often resulting from respiratory distress or asphyxia as compared with myocardial dysfunction in adults. The optimal method for resuscitation of children remains uncertain. For adults, significant advances have been made in the acute care of cardiac arrest, such as the use of vasopressin, and post resuscitation care, such as induced hypothermia. High-dose epinephrine in adult cardiac arrest is still occasionally employed but has largely fallen out of favor and data in its support are lacking. The American Heart Association recommendation that rescue doses of epinephrine in children be "high-dose" and 0.1 mg/kg was largely on the basis of a retrospective study of pediatric in-hospital cardiac arrest. However, subsequent studies have failed to document significantly improved outcomes with higher-dose epinephrine compared with standard-dose epinephrine. Based on the results of this trial, it appears that high-dose epinephrine should also be abandoned in the resuscitative efforts of pediatric cardiac arrest.

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