

Paper reports

Synopses of recently published research relevant to intensivists

6 November 2001 – 8 January 2002

Overview

Sepsis, insulin and noninvasive ventilation

Richard Venn

Critical Care 2002, **6**:93-94

The paper reports presented here reflect the current leading issues in the intensive care literature, the search for the 'magic bullet' in sepsis being an obvious example. Many of the trials in sepsis that are currently being reported were presented at recent conferences [1]. This is the case for the KyperSept Antithrombin III Study (see paper report) [2]. The summary of this paper highlights the disappointment of the study: "ATIII [antithrombin III] joins a long list of promising experimental agents for sepsis that failed to show a significant benefit in a multicentre, randomised phase III clinical trial."

Although some success has been reported with 'magic bullet' studies [3], the paper by Rivers and colleagues (see paper report) [4] puts these to shame by demonstrating a superlative outcome benefit with essentially good early resuscitative care in severe sepsis and septic shock. Goal-directed therapy in the emergency department for patients with severe sepsis and septic shock improved survival from 46.5% (control) to 30.5% (goal-directed therapy). This was achieved by targeting central venous saturation – an investigation that could easily be performed in most modern emergency departments – and the resultant treatment was by no means complicated or expensive: increased fluids and/or blood, and occasionally dobutamine for inotropic support. That study mirrors the already impressive and abundant evidence for goal-directed therapy in another patient population – the high-risk surgical patient [5]. It is incredible, yet disconcerting, that a relatively basic but successful and cheap treatment for the high risk or critically ill patient is not current practiced in many intensive care units. However, the expensive practice of magic bullets will no doubt be enthusiastically received, despite the fact that the results are far less impressive. The report of Rivers and colleagues [4] emphasizes the enormous benefits that may be achieved by early, good, basic critical care management.

The benefits of noninvasive ventilation once again feature prominently in our paper reports [6]. Patients with acute hypoxaemic respiratory failure following lung resection were randomized to standard care with or without nonintermittent positive

pressure ventilation. Not surprisingly, the need for extubation was significantly higher in the control group, as was hospital and 120-day mortality. It would be interesting to know whether this mortality benefit remained significant if the randomization had been to nonintermittent positive pressure ventilation versus invasive ventilation.

Hormone therapy has always been popular in the critically ill, and one report [7] investigated intensive insulin therapy in non-diabetic surgical and critically ill patients. Crude hospital mortality was 7.2% in the intensive therapy group versus 10.9% in the control group ($P = 0.01$), and this benefit was associated with a 46% reduction in bloodstream infections.

Finally a Canadian study [8] derived the 'Canadian C-spine rule' in order to allow more selective and specific ordering of C-spine X-rays in trauma patients who are alert and stable. The derived rule had a sensitivity of 100% and specificity of 42.5%.

As was highlighted in the first paper report overview published back in November 1999 [9], there has been an exponential growth in the amount of literature specific to intensive care and related fields. "This is set against the background of an ever-increasing service commitment and so time is at a premium to reflect on important breakthroughs in the literature," it said. Our paper reporters, who are few in number as compared with the amount of evidence based literature out there, are not immune to these time constraints. If you, the reader, would like more papers critiqued, or even to join our 'merry band of reporters', contact us on editorial@ccforum.com.

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Paper reports

C-spine rule for radiography in trauma patients

Stiell IG, Wells GA, Vandemheen KL, Clement CM, Lesiuk H, De Maio VJ, Laupacis A, Schull M, McKnight RD, Verbeek R, Brison R, Cass D, Dreyer J, Eisenhauer MA, Greenberg GH, MacPhail I, Morrison L, Reardon M, Worthington J: **The Canadian C-Spine Rule for Radiography in alert and Stable Trauma Patients.** *JAMA* 2001, **286**:1841-1848.

Topic: Audit and management, Scoring/outcome, Trauma

Reported by: Arpan Guha

Paper report publication date: 4 January 2002

Keywords: injury, cervical spine; radiological imaging; alert, stable trauma patients

Level of evidence: Level V

Context: The cervical spine (C-spine) of trauma victims has been routinely imaged radiologically to rule out bony injury. Many trauma experts find this exercise unnecessary in the majority of cases who are alert, and without clinical suspicion of injury. This study has three aims: to evaluate the possibility of being more selective and specific in ordering C-spine X-rays in trauma patients who are alert and stable; to examine possible predictor variables against actual patient outcome; and to provide a 'rule' that will be clinically effective in decision-making.

Significant findings: A variety of data were collected from patients with blunt trauma. These variables (e.g. mechanism of injury, neck pain, whether radiography was performed, etc) were then analyzed to find the best combination of predictor variables for detecting clinically important C-spine injury with high sensitivity and specificity. This information was used to derive a rule, which was validated by comparing the classification of patients to their actual status.

Radiology identified clinically significant C-spine injury in 151 (1.7%) patients. The derived rule identified these with a sensitivity of 100% (95% confidence interval) and a specificity of 42.5 % (95 % CI). The authors were able to provide recommendations for situations where C-spine radiography is warranted so that resources are used efficiently without jeopardising patient care. Finally, they derived the present 'Canadian C-spine rule'.

Comments: At present there is no well defined algorithm based on research that would allow clinicians to minimise radiological imaging of the C-spine without putting patients at risk. This study attempts to fill that gap in our practice.

There is a potential to miss clinically unimportant (i.e. spinal injury that requires neither stabilization, nor follow up). There were also some patients in the study who did not undergo C-spine radiography if the attending doctors felt that it was not warranted (which is normal practice in Canada).

Methods: A total of 8924 adult patients with significant acute blunt trauma to the head or neck presented to the Emergency Departments of 10 large Canadian community and University hospitals, these were studied as a prospective cohort. Patients were alert and stable as defined by cardiorespiratory parameters.

The primary outcome measure was the incidence of clinically important C-spine injury. Patients underwent plain radiography of the C-spine and some also had flexion-extension views and CT of the C-spine. Patients who did not have any diagnostic radiological imaging were followed up for 14 days.

The golden hours of septic shock?

Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M: **Early goal directed therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345**:1368-1377.

Topic: Monitoring, Scoring/Outcome, Sepsis

Paper report publication date: 19 December 2001

Reported by: Jeremy Bewley

Keywords: Sepsis, septic shock, resuscitation, treatment, mortality, outcome

Level of evidence: Level I

Context: Goal directed haemodynamic optimisation has been demonstrated to increase mortality when initiated on the intensive care unit (ICU). This study is original as it recruits patients particularly early, in the hospital emergency department before admission to the ICU. Secondly it uses central venous saturation as the resuscitation end point.

Significant findings: A reduced hospital mortality was found in the treatment of severe sepsis, from 46.5% with standard treatment to 30.5% with early goal directed therapy. The proposed reason for this was a significantly higher mean central venous saturation (77% vs 66%). This was achieved through increased use of fluids (5 litres vs 3.5 litres), blood (64% vs 19%), and dobutamine (14% vs 1%) during the first 6 hours of care in the emergency department.

Comments: This is a well-designed randomised study that addresses the important question of resuscitation of patients

with septic shock. It is not easy to blind clinicians in such a study so bias is possible, especially as many of the patients in the treatment arm spent longer in the emergency department and received blood transfusions. This study demonstrates that increased administration of fluids and more controversially blood can reduce mortality when administered early. Dobutamine was only administered to a relatively small number of patients whilst there was no difference in the use of other vasopressors. The value of central venous saturation monitoring could be debated as a target central venous pressure (CVP) of 12–16 mmHg may have achieved the same results. Despite this the study demonstrates that early aggressive resuscitation is successful in reducing mortality and can be undertaken with the use of simple resuscitation end points. Studies of longer duration and using other centres would be valuable for confirming this benefit.

Methods: 263 patients with severe sepsis who were either in a state of shock or had a lactate >4 mmol/l were randomised between an initial 6 hours of either early goal directed therapy or standard therapy. Both groups were managed with arterial and central venous monitoring. The goal directed group had a target central venous saturation of >70% in addition to the standard targets of central venous pressure (CVP) 8–12 mmHg, mean arterial pressure 65–90 mmHg, and urine output >0.5 ml/Kg/min.

Additional information: Accompanying editorial: Evans T: **Hemodynamic and Metabolic Therapy in Critically Ill Patients.** *N Engl J Med* 2001, **345**:1417-1418.

Antithrombin III and sepsis

Warren BL, Eid A, Singer P, Pillay SS, Carl P, Novak I, Chalupa P, Atherstone A, Péntzes I, Kübler A, Knaub S, Keinecke H-O, Heinrichs H, Schindel F, Juers M, Bone RC, Opal SM, for the KyberSept Trial Study Group: **High-dose antithrombin III in severe sepsis: a randomised controlled trial.** *JAMA* 2001, **286**:1869-1878.

Topic: Pharmacology, Scoring/Outcome, Sepsis

Reported by: Richard Venn

Paper report publication date: 14 November 2001

Keywords: Antithrombin III, outcome, sepsis

Level of evidence: Level 1

Context: Uncontrolled activation of the coagulation system may contribute to the mortality associated with septic shock. This phase III multicentre trial investigated the role of antithrombin III (ATIII), a serine protease inhibitor affecting multiple aspects of the coagulation cascade, in patients with severe sepsis and septic shock.

Significant findings: The baseline ATIII activity was approximately 60% in both groups. This rose to 180% in ATIII group at 24 hours; there was no change in the placebo group at 24 hours.

Overall mortality at 28 days was 38.9% in the ATIII group versus 38.7% in the placebo group; similarly, there was no difference at 90 days.

Statistical evidence for interaction between heparin and ATIII can be derived from multiple logistic regression analysis. There was a significant mortality benefit at 90 days for patients not receiving heparin: 352 (49%) in the ATIII group versus 346 (52.5%) in the placebo group ($P = 0.03$).

Overall there was no difference between groups except for bleeding events, which had an incidence of 22% in the ATIII group and 13% in the placebo group ($P < 0.001$); this was most marked in patients receiving concomitant heparin therapy.

Comments: The summary to this paper highlights the disappointment of this study: ATIII "joins a long list of promising experimental agents for sepsis that failed to show a significant benefit in a multicenter, randomised phase III clinical trial". Patients treated in this study with ATIII demonstrated lower ATIII activity (180%) than was expected from preclinical trials (200–250% activity), which may have contributed to the absence of clinical outcome benefit. Another explanation for this lack of benefit is that heparin competitively inhibits binding of ATIII for glycosaminoglycans on the endothelial surface of inflammatory cells, which would explain why those patients without concomitant heparin therapy had an outcome advantage with ATIII over placebo. Adverse bleeding events are obviously a concern in severe sepsis patients receiving ATIII.

Despite the negative result, ATIII will continue to fascinate the intensivist, and it may be that a subgroup of severe sepsis patients will benefit from this therapy once the optimum dosage regime has been determined.

Methods: This was a double-blind, multicentre, phase III, randomised placebo-controlled trial in which 2314 patients with severe sepsis were randomised to receive 30,000 IU ATIII or placebo.

Exclusions included known bleeding disorders, and heparin therapy – except low-dose (<10,000 IU/day) subcutaneous heparin or intravenous line flushing with heparin.

Tight glucose control in the critically ill improves survival

Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: **Intensive insulin therapy in critically ill patients.** *N Engl J Med* 2001, **345**:1359-1367.

Topics: Outcome

Reported by: Ognjen Gajic

Paper report publication date: 21 November 2001

Keywords: Hyperglycemia, multiple organ failure

Level of Evidence: Level I

Context: Stress induced hyperglycemia is common in critically ill patients and may be associated with an increased rate of infectious complications (see Additional information [1]). Harmful effects of growth hormone therapy (see Additional information [2]) and parenteral nutrition (see Additional information [3]) may be related, at least in part, to the prevalence of hyperglycemia in critically ill patients. Intensive glucose management has been shown to improve survival in patients with diabetes mellitus and acute myocardial infarction (see Additional information [4]). This controlled trial investigates glucose management in nondiabetic surgical and critically ill patients.

Significant findings: In total, 1548 patients were enrolled. There were no significant differences between the intensive-therapy group and control group at randomization.

Following intervention the mean morning glucose levels were 103 mg/dl in the intensive-therapy group versus 153 mg/dl in the control group. Crude hospital mortality was 7.2% in the intensive-therapy group and 10.9% in the control group ($P=0.01$). The benefit was even more significant in the subgroup of patients receiving intensive care for >5 days (mortality rate 16.8% versus 26.3%). The mortality benefit was associated with a 46% decrease in bloodstream infections.

Comments: Although nonblinded and restricted to patients undergoing cardiac surgery this study will, in all likelihood, have a great impact on the management of critically ill patients. For diabetic patients with acute myocardial infarction and for patients with or without diabetes mellitus recovering from cardiac surgery, data appear strong. There is no reason to believe this would not be applicable to critically ill patients in general.

Methods: Patients receiving mechanical ventilation in a cardiac surgery intensive care unit were randomized to conventional (insulin drip only if blood glucose level above 200 mg/dl) and strict glucose control (insulin drip to maintain normal blood glucose level(80-110 mg/dl).

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There is an editorial in the same issue: Evans TW: **Hemodynamic and metabolic therapy in critically ill patients.** *N Engl J Med* 2001, **345**:1417-1418.

Noninvasive ventilation after lung resection

Auriant I, Jallot A, Herve P, Cerrina J, Le Roy Ladurie F, Fournier JL, Lescot N, Parquin F: **Noninvasive ventilation reduces mortality in acute respiratory failure following lung resection.** *Am J Respir Crit Care Med* 2001, **164**:1231-1235.

Topics: Respiratory, Surgery, Outcome

Reported by: Ognjen Gajic

Paper report publication date: 21 November 2001

Keywords: Pneumonectomy, respiratory failure, ventilation

Level of Evidence: Level II

Context: When compared with the usual regime of oxygen supplementation, noninvasive positive pressure ventilation (NIPPV) has been shown to have a number of advantages: it can decrease the need for endotracheal intubation in unselected patients with acute respiratory failure (see Additional information [1]); in immunosuppressed patients it can decrease ICU mortality (see Additional information [2]); and in a small group of patients that had undergone lung resection it resulted in improved gas exchange without undesirable effects (see Additional information [3]). NIPPV should not be confused with continuous positive airway pressure, which has not been shown to be of benefit in patients with acute hypoxemic respiratory failure (see Additional information [4]). This study compares outcomes of either NIPPV or standard oxygen supplementation in patients who have undergone lung resection.

Significant findings: A total of 48 patients were prospectively enrolled (24 in each arm). The study was stopped prematurely because of a significant difference in the primary outcome measure, need for endotracheal intubation (20.8% versus 50%, $P=0.035$). The hospital mortality (12.5% versus 37.5%, $P=0.045$) and 120-day mortality (12.5% versus 37.5%) were lower in the NIPPV group. There was no significant difference in either the length of ICU ($P=0.52$) or hospital ($P=0.61$) stay.

Comments: This study supports the trend in current practice towards earlier use of NIPPV in patients with acute respiratory failure. The earlier decrease in the work of breathing and avoidance of complications associated with endotracheal intubation (e.g. infection, sedation, ventilator induced lung injury and barotrauma) are likely reasons for the observed decrease in mortality. As in other NIPPV studies, patients who experienced hemodynamic stability, excessive secretions, agitation, or extreme respiratory distress were excluded from the study.

Methods: Patients with acute hypoxemic respiratory failure after lung resection were randomized to usual care (oxygen, bronchodilators, chest physiotherapy) with or without NIPPV. The study was not blinded. The primary outcome was the need for endotracheal intubation. Secondary outcomes were hospital and 120-day mortality, and duration of hospital and ICU stay.

Additional Information:

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