

Commentary

Recently published papers: *Pseudomonas*, brain and bowel injury and novel cardiac therapies

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Critical Care 2008, **12**:184 (doi:10.1186/cc7019)**Abstract**

Ventilator-associated pneumonia is a familiar foe in intensive care units, but those associated with *Pseudomonas aeruginosa* have a particularly adverse impact on outcome. Correct antibiotic therapy and a novel endotracheal tube may reduce this burden. Does activated protein C improve outcome from acute lung injury and what is the role played by hyperventilation therapy in traumatic brain injury? Recent research has attempted to answer these questions. Further novel approaches have been evaluated in the management of ischaemic heart disease, and more light has been shed on acute bowel injury.

empirical antibiotic policies in VAP in the case of higher rates of VAP due to antibiotic-resistant bacteria.

In a second report, El Solh and colleagues [6] suggested that short-course (≤ 7 days) antimicrobial therapy may not be adequate. The investigators studied the high mortality figures in *Pseudomonas* VAP and evaluated causes of microbial persistence in the alveolar space despite adequate antimicrobial therapy. They hypothesized that failure to eradicate *P. aeruginosa* from the lung is linked to type III secretory system isolates (cytotoxins indicating virulence). Thirty-four patients with *P. aeruginosa* VAP underwent noninvasive BAL at the onset of VAP and on day 8 after initiation of antibiotic therapy. Analysis for type III cytotoxins was undertaken and results indicated that about 50% of the patients had persistence of type III secretory system cytotoxins. The rest had full eradication, with undetectable levels of the cytotoxins. The persistence of the cytotoxins was attributed to the delay to eradication of the micro-organisms, and hence the recommendation is for longer courses of antimicrobial therapy.

Ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is strongly associated with adverse outcomes in mechanically ventilated patients in the intensive care unit (ICU). Its incidence is about 8% to 20% [1] and mortality ranges between 20% and 50% [2]. Consequently, VAP has considerable impact on morbidity, length of stay and cost of ICU care [3,4].

Kollef and coworkers [5] conducted a retrospective cohort study involving 76 patients in an urban tertiary hospital who were recruited over 5 years. The objective was to identify predictors of 30-day mortality and hospital costs in patients with VAP attributed to potentially antibiotic-resistant Gram-negative bacteria (*Pseudomonas aeruginosa*, *Acinetobacter* spp. and *Stenotrophomonas maltophilia*). Overall mortality was 25%. Patients receiving their first dose of appropriate antibiotic therapy within 24 hours of bronchoalveolar lavage (BAL) sampling had a statistically lower 30-day mortality rate and hospitalization cost as compared with patients receiving their first dose of appropriate therapy more than 24 hours after BAL (17.2% versus 50.0%). The authors conclude that prompt (< 24 hours) microbiological diagnosis and appropriate initial antimicrobial therapy produced healthier outcome data; and that appropriate changes should be made to local

Kollef and coworkers produced another report from the NASCENT trial [7], which is a multicentre randomized single blinded study including about 2,003 patients considered for the trial. The primary outcome was the incidence VAP by means of BAL fluid analysis at 24 hours. Patients were assigned to undergo intubation with one of two high-volume, low-pressure endotracheal tubes (ETT), which were similar except for a silver coating on the experimental tube. The microbiologically confirmed rate of VAP in the treatment limb was 4.8% and that in the conventional limb was 7.5%, with a relative risk reduction of 35.9%. The investigators suggested that patients receiving a silver-coated ETT had a statistically significant reduction in the incidence of VAP and delayed time to VAP occurrence as compared with those receiving a similar, uncoated tube, although there was not much impact

ALI = acute lung injury; APC = activated protein C; BAL = bronchoalveolar lavage; ETT = endotracheal tube; IAH = intra-abdominal hypertension; IAP = intra-abdominal pressure; ICU = intensive care unit; TBI = traumatic brain injury; VAP = ventilator-associated pneumonia.

on length of stay and overall mortality. Does this provide a rationale for using silver-lined ETTs in patients who are likely to require ventilation for longer than 24 hours?

Finally, we examine another paper published in *Critical Care Medicine* [8] dealing with outcome data from VAP patients with high bacterial loads. The authors investigated the frequency and outcomes of ventilated patients with newly acquired, large-burden infection with *P. aeruginosa*. They also verified the hypothesis that large bacterial loads were associated with adverse outcomes. A total of 69 patients were enrolled into the prospective study over a 4-year period who required more than 48 hours of mechanical ventilation and were identified as having newly acquired *P. aeruginosa* in their lower respiratory tracts. Daily surveillance cultures of endotracheal aspirates, *Pseudomonas* quantification and clinical signs of infection were analyzed. The results make for interesting reading. Forty-five out of 69 patients had high *Pseudomonas* burdens, but about one-third of these did not meet clinical criteria for VAP diagnosis but still had statistically significant higher risk for death (adjusted hazard ratio = 37.53) as compared with the patients who had clinically diagnosed *P. aeruginosa* VAP. Furthermore, more patients with high *P. aeruginosa* burdens secreted the type III secretion facilitator protein PcrV, suggesting higher virulence. Is it time to revisit the clinical criteria for VAP diagnosis, with greater emphasis on quantification of respiratory tract bacterial load?

Hyperventilation therapy after traumatic brain injury

Neumann and coworkers reported data from the BrainIT database concerning use of hyperventilation strategies and adherence to Brain Trauma Foundation Guidelines after traumatic brain injury (TBI) in intensive care medicine [9]. This was a retrospective study of monitoring data from 22 European centres and involved 151 patients. The latest editions of the Brain Trauma Foundation Guidelines maintain a restricted use of hyperventilation for the treatment of TBI because of its negative impact on cerebral blood flow/oxygenation and clinical outcome [10,11]. The study utilized data from nearly 8,000 blood gas analyses, representing ventilation episodes along with related minute by minute intracranial pressure data. Episodes were studied as under 24 hours or over 24 hours since TBI. Results from the study indicate that there was general adherence to guidelines except in cases of early prophylactic hyperventilation and cerebral oxygenation monitoring in forced hyperventilation. The authors suggest that, in the absence of elevated intracranial pressure, hyperventilation is better avoided; and that intentional reduction in arterial carbon dioxide tension to below 35 mmHg has little supporting evidence.

Acute lung injury

Use of activated protein C (APC) in severe sepsis following the PROWESS and ADDRESS studies received a major

boost throughout the world in all major ICUs. APC is a recognized adjunctive therapy in severe sepsis along with best standard care. It has been widely accepted that plasma protein C levels are low in patients with acute lung injury (ALI) (even without sepsis), with higher mortality/morbidity figures [12].

A report recently published in the *American Journal of Respiratory and Critical Care Medicine* [13] examined the efficacy of APC as a therapy for patients with ALI. American/European consensus criteria for ALI were used to identify suitable patients, and those with severe sepsis and an Acute Physiology and Chronic Health Evaluation II score of 25 or greater were excluded. The primary end-point was ventilator-free days. Eligible patients were randomly assigned to either receive APC or placebo (double blinded) within 72 hours. The results revealed that the APC-treated group had increased plasma protein C levels and decreased pulmonary dead space fraction, but sadly this did not translate into clinical benefit, there being no difference in the number of ventilator-free days between the two groups. Hence, the investigators concluded that APC did not improve outcomes from ALI in the absence of severe sepsis and high disease severity.

Current affairs in ischaemic heart disease

Results from BEAUTIFUL [14], a randomized, double-blind, placebo-controlled trial evaluating the use of ivabradine for patients with stable coronary artery disease and left ventricular systolic dysfunction, were recently published in the *Lancet*.

Ivabradine specifically inhibits the *I_f* current in the sinoatrial node to lower heart rate. Fox and coworkers [14] exploited this effect of the drug in more than 10,000 patients with stable coronary artery disease and left ventricular ejection fraction less than 40% recruited over 2 years. The primary end-point was a composite of cardiovascular death, admission to hospital for acute myocardial infarction and admission to hospital for new onset or worsening heart failure. The results indicated that the drug did not improve primary end-points but improved secondary end-points. The investigators suggested that use of the drug in patients with higher heart rates (more than 70 beats/minute) reduced the incidence of coronary artery disease outcomes.

'On-TIME 2' data were also recently published in the *Lancet* [15]. This was a multicentre, double-blind trial including 984 patients, who were randomly assigned to receive tirofiban (GpIIb/IIIa inhibitor) and placebo. The primary end-point was the extent of residual ST-segment deviation 1 hour after percutaneous coronary intervention. The study identified significant benefit from prehospital use of tirofiban in patients with acute ST-segment elevation myocardial infarction undergoing primary coronary angioplasty (percutaneous coronary intervention).

Acute bowel injury

Reintam and coworkers [16] reported findings from a study in which they evaluated the differential impact of primary and secondary intra-abdominal hypertension (IAH) on outcomes in intensive care medicine. This was a prospective study of 257 mechanically ventilated patients deemed to be at considerable risk for development of IAH. These patients underwent repeated measurements of intra-abdominal pressure (IAP) during their ICU stay and were followed up to 90-day survival. The authors incorporated the new consensus definitions recently established by the World Society of the Abdominal Compartment Syndrome [17].

- IAH is sustained or repeated pathological elevation of IAP to 12 mmHg or greater.
- Abdominal compartment syndrome is sustained IAP above 20 mmHg along with a new organ dysfunction.
- Primary IAH is a condition associated with injury or disease in the abdomino-pelvic region that frequently requires early surgical or interventional radiological intervention (for example, peritonitis, pancreatitis, bowel disease, or abdominal trauma).
- 'Secondary IAH' refers to conditions that do not originate from the abdomino-pelvic region (for example, sepsis/shock, polytrauma, cardiopulmonary disease, intoxications, or burns).

IAH developed in 95 patients (37.0%) with primary IAH ($n=60$) and secondary IAH ($n=35$) [16]. Patients with secondary IAH exhibited a significant increase in mean IAP during the first 3 days, whereas IAP decreased in the patients with primary IAH. The patients with IAH had a significantly higher mortality compared with patients without the syndrome. The authors concluded the following: secondary IAH is less frequent, has a different time course and worse outcome; IAH was an independent predictor of ICU adverse outcome; and ICU patients with two or more risk factors should undergo daily IAP measurement.

This study was accompanied by an excellent editorial review [18] that highlighted the importance of understanding the mechanism of injury in IAH/abdominal compartment syndrome. The review also proposed the concept of acute bowel injury and acute intestinal distress syndrome. Clearly, much work needs to be done in this area.

Competing interests

The authors declare that they have no competing interests.

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