Critical Care Year in Review: The Latest in Mechanical Ventilation, Sepsis, and ARDS

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MECHANICAL VENTILATION

Robert Hyzy, MD, University of Michigan, Ann Arbor, Michigan, USA, discussed advances in mechanical ventilation. Nonbenzodiazepine sedatives propofol or dexmedetomidine have been preferred over benzodiazepine sedatives midazolam or lorazepam to improve clinical outcomes [Barr J et al. *Crit Care Med.* 2013]. A definitive randomized controlled trial (RCT) comparing propofol and midazolam or lorazepam is unlikely, in light of a multicenter retrospective cohort study in which ventilated intensive care unit (ICU) patients who were sedated exclusively with propofol, midazolam, or lorazepam reported improved outcomes with propofol, including greater likelihood of ICU discharge and earlier discontinuation of ventilator use (Table 1) [Lonardo NW et al. *Am J Respir Crit Care Med.* 2014].

For oxygen ventilation in acute respiratory distress syndrome (ARDS), lower saturation has been associated with worse cognitive outcome, while a higher than necessary level of oxygen can worsen lung inflammation [Aggarwal NR, Brower RG. *Ann Am Thorac Soc.* 2014]. The use of a conservative strategy of oxygen ventilation was linked with a trend to lower lactate and reduced failure of nonpulmonary organs [Suzuki S et al. *Crit Care Med.* 2014]. The single-center nature of the study and small number of patients prevent any definitive conclusion. An RCT would be helpful.

A recent study involving 20 patients indicated that draining of pleural effusions improves oxygenation via increased lung volume and decreased transpulmonary pressure, although the benefit was less pronounced with ARDS patients [Razazi K et al. *Ann Am Thorac Soc.* 2014].

Finally, an RCT involving 105 patients provided evidence that a nasally delivered elevated oxygen level provides better oxygenation and improves patient outcome compared with the use of a ventilation mask [Maggiore SM et al. *Am J Respir Crit Care Med.* 2014].

SEPSIS AND RESUSCITATION

Steven Simpson, MD, University of Kansas Medical Center, Kansas City, Kansas, USA, discussed several recent trials that addressed sepsis and resuscitation. The multicenter, randomized controlled Protocolized Care for Early Septic Shock trial [ProCESS; ProCESS Investigators. *N Engl J Med.* 2014] was undertaken to investigate the need for central lines for hemodynamic and central venous oxygen saturation ($ScvO_2$) monitoring, and the need for protocol-determined care.

The 1341 patients were randomized to receive early goal-directed therapy (EGDT; n = 439), a standard therapy protocol (n = 446), and usual care (n = 456). The three arms were comparable at baseline in demographics, source of sepsis, and other clinical aspects. The primary outcome was 60-day all-cause mortality. Secondary outcomes included 90-day all-cause mortality, 90-day and 1-year cumulative mortality, length of stay in the hospital and the ICU, duration of shock, acute respiratory failure, acute renal failure, and hospital discharge disposition.

The primary end point did not differ significantly among the study arms (log-rank $P = .52$). Outcomes were similar with the exception of a greater rate of ICU admission in those receiving EGDT ($P = .01$).

The randomized, controlled Australasian Resuscitation in Sepsis Evaluation trial [ARISE; ARISE Investigators. *N Engl J Med.* 2014] was done to assess the value of EGDT in decreasing mortality in patients with septic shock. The 1600 patients enrolled at 51 centers were randomized to receive EGDT (n = 796) or usual care (n = 804). The primary outcome was 90-day all-cause mortality, and there were multiple secondary and tertiary outcomes. Analyses were conducted in

Table 1. Outcomes With Propofol

Outcomes	Midazolam Matched (n = 2250)	Propofol Matched (n = 2250)	*P* Value	Relative Risk (95% CI)	Lorazepam Matched (n = 1054)	Propofol Matched (n = 1054)	*P* Value	Relative Risk (95% CI)
ICU mortality	28.8	19.7	< .001	0.69 (0.62 to 0.76)	25.2	19.3	.001	0.76 (0.65 to 0.90)
Hospital mortality	37.0	27.9	< .001	0.76 (0.69 to 0.82)	33.8	26.2	< .001	0.78 (0.68 to 0.89)
Tracheostomy	14.04	14.09	.967	1.00 (0.87 to 1.16)	21.82	14.99	< .001	0.69 (0.57 to 0.83)
Ventilator-associated pneumonia	6.2	6.8	.43	1.09 (0.88 to 1.36)	12.7	7.9	< .001	0.62 (0.48 to 0.80)

Data are given as the percentage of patients unless otherwise indicated.

ICU, intensive care unit.

Table 2. Primary Outcome of 90-Day All-Cause Mortality in ARISE

Outcome	Value
Early goal-directed therapy, %	18.6
Usual care, %	18.8
Relative risk (95% CI)	0.98 (0.80 to 1.21)
Risk difference (95% CI)[a]	−0.3 (−4.1 to 3.6)
P value	.90

[a]Risk differences of < 1.0 indicate better results in the early goal-directed therapy group.

Source: Peake SL et al. *New Engl J Med.* 2014.

the intention-to-treat population. The study arms were comparable at baseline.

Patients in the EGDT group received more intravenous fluids in the first 6 hours after randomization than patients treated with usual care (1964 ± 1415 mL vs 1713 ± 1401 mL; $P < .001$). EGDT patients were more likely to receive vasopressor infusions (66.6% vs 57.8%), red-cell transfusions (13.6% vs 7.0%), and dobutamine (15.4% vs 2.6%) (*P* for all, $P < .001$).

The primary outcome was comparable between the groups (Table 2), meaning that EGDT did not reduce all-cause mortality. There was no significant difference in survival time, in-hospital mortality, duration of organ support, or length of hospital stay.

The negative results of ProCESS and ARISE do not represent the final word on EGDT, for a number of interrelated reasons. The patients studied in both trials had lower measured lactate and higher $ScvO_2$ than in the original EGDT trial, and Acute Physiology and Chronic Health Evaluation II scores were lower in the ARISE trial. Among the patients in the EGDT arm of both studies, the average $ScvO_2$ was 71%; for the substantial proportion of patients with $ScvO_2$ measures above 70%, the protocol did not specify therapeutic actions. In other words, these patients defaulted to usual or standard care. It would therefore be difficult to demonstrate differences between this group and the group with intended standard care, requiring significantly more patients than were studied in either trial. Neither trial reports whether there were benefits to EGDT in the patients whose measured baseline $ScvO_2$ was under 70%.

The multicenter, open-label ALBIOS trial [Caironi P et al. *N Engl J Med.* 2014] assessed the value of albumin replacement in patients with severe sepsis or septic shock. The ≥ 1800 patients treated at 100 ICUs were randomized to 20% albumin + crystalloid solution or crystalloid solution alone. The target serum albumin was ≥ 30 g/L. The primary outcome was 28-day all-cause mortality; secondary outcomes were 90-day all-cause mortality, organ dysfunctions, and length of hospital and ICU stay.

Patients receiving albumin had a higher 7-day mean arterial pressure ($P = .03$) and lower net fluid balance ($P < .001$). However, the total daily amount of administered fluid was comparable between groups ($P = .10$), as was the primary outcome and the 90-day all-cause mortality. Thus, albumin replacement did not appear to be of value in aiding survival.

NONRESPIRATORY CRITICAL CARE

David L. Bowton, MD, Wake Forest University Baptist Health, Winston-Salem, North Carolina, USA, discussed advances in nonrespiratory critical care. A number of recent studies including ProCESS and ARISE have the

potential to inform the care of patients with severe sepsis and septic shock.

Two retrospective observational studies assessed the amount and timing of use of vasopressors and fluids on hospital mortality. The CATTS study of 2849 patients from 24 ICUs chronicled decreased mortality when vasoactive agents were commenced 1 to 6 hours after onset of septic shock, especially when fluids were applied within the first hour [Waechter J et al. *Crit Care Med.* 2014]. Another study of 651 patients with severe sepsis and septic shock revealed a survival benefit in those receiving fluid resuscitation within 3 hours of ICU admission [Lee SJ et al. *Chest.* 2014].

A trio of studies collectively involving ≥ 13 000 patients reported the association of hyperchloremia and the use of normal saline rather than balanced crystalloids with higher mortality and incidence of renal failure [McCluskey SA et al. *Anesth Analg.* 2013; Shaw AD et al. *Ann Surg.* 2012; Yunos NM et al. *JAMA*. 2012]. However, in a study of the effects of balanced vs nonbalanced fluids, a propensity-matched cohort of 6730 patients (of 53 448 patients total) reported a lower risk of in-hospital mortality in adult patients critically ill with sepsis who were resuscitated with balanced fluids [Raghunathan K et al. *Crit Care Med.* 2014].

A multicenter, open-label study involving 776 patients addressed resuscitation in septic shock from the standpoint of blood pressure [Asfar P et al. *N Engl J Med.* 2014]. Patients were randomized to a mean arterial pressure target of 80 to 85 mmHg (high-target; n = 388) or 65 to 70 mmHg (low target; n = 388). There was no difference in the primary end point of 28-day mortality, although high-target patients with chronic hypertension required less renal replacement therapy.

If definitive conclusions cannot yet be reached, the data highlight the importance of every hospital having a treatment process, with clear goals and treatments.

The final topic addressed by Dr Bowton was parenteral vs enteral nutrition. The CALORIES trial [Harvey SE et al. *N Engl J Med.* 2014] of 2400 patients in the United Kingdom found no difference in outcome between the study arms in terms of 30-day all-cause mortality. The MetaPlus prospective randomized clinical trial [van Zanten ARH et al. *JAMA*. 2014] of 301 adult, mechanically ventilated patients who required enteral nutrition for over 72 hours reported no difference between high-protein enteral nutrition with immune-modulating nutrients and standard high-protein enteral nutrition concerning infectious complications, with possible increased mortality for the immune-modulating regimen. The studies support the view that the route of feeding is not as important as was previously thought; patients should be fed with nutrition that is tolerable and cost-effective, as full caloric feeding has shown little value.

ARDS

Arthur Wheeler, MD, Vanderbilt University, Nashville, Tennessee, USA, reviewed recent developments in the treatment of ARDS. The multicenter, double-blind SAILS trial [National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. *N Engl J Med.* 2014] involving 745 patients with sepsis-associated ARDS evaluated rosuvastatin vs placebo. The trial was stopped for futility, with no difference between the groups in the assessed outcomes. Similarly, the double-blind HARP-2 trial [McAuley DF et al. *N Engl J Med.* 2014] involving 540 patients reported no appreciable difference between treatment with simvastatin and placebo concerning the primary outcome of ventilator-free days and secondary outcomes of organ failure-free days and 28-day mortality. Other trials have indicated the futility of statins for prevention of ARDS, or treatment of ventilator-associated pneumonia [Yadav H et al. *Anesth Analg.* 2014; Papzian L et al. *JAMA*. 2013].

Interestingly, it is possible that patients with worse clinical outcomes due to more severe inflammation, shock, and metabolic acidosis — a hyperinflammatory phenotype — may be more receptive to positive end-expiratory pressure (PEEP) therapy [Calfee CS et al. *Lancet Respir Med.* 2014]. In a related study, patients with an increase in the ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen after a transient increase in PEEP may have a survival advantage, potentially leading to a bedside maneuver to identify patients with a better prognosis [Goligher EC et al. *Am J Respir Crit Care Med.* 2014].

Two meta-analyses suggest use of prone positioning may be advantageous, especially in ARDS patients receiving protective lung ventilation [Lee JM et al. *Crit Care Med.* 2014; Sud S et al. *CMAJ.* 2014; Guérin C et al. *N Engl J Med.* 2013], which is consistent with the benefits of lower tidal volume.

While there have been advances in care of ARDS patients and improvements in outcome, accumulating data indicate that ARDS survivors remain sick for a long time and in some respects, ARDS may essentially be a life sentence.