Brief Review

2018 Year in Review in Critical Care

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The objective of this review is to highlight major randomized controlled trials (RCTs) in critical care in 2018. Through literature search, we identified 16 studies published in the year 2018 in high impact medical journals. These studies have been chosen based on the significance and the relevance of questions addressed and on the methodology. Common features among these studies include the large number of patients, being multicenter and multinational and the generalizability of the results to multiple and heterogeneous settings. The articles were grouped based on major area of focus and the clinical question that has been investigated.

Table 1 summarizes PICO (Patients, intervention, comparison and outcome) questions of the included studies.

Steroids

Septic shock may be associated with relative adrenal insufficiency. Low-dose hydrocortisone was found in one trial to reduce the risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse events.[1] However, later studies did not confirm this finding.[2-4]

The recent ADRENAL trial[5] compared hydrocortisone 200 mg/day, given as continuous infusion for 7 days or until intensive care unit (ICU) discharge to placebo. The trial included 3658 patients from 69 medical-surgical ICUs across Australia, the UK, New Zealand, Saudi Arabia, and Denmark between March 2013 and April 2017. The trial found that 511 of 1832 patients (27.9%) in the hydrocortisone died by day 90 versus 526 of 1826 (28.8%) in the placebo group with no statistical difference (Odds ratio [OR], 0.95; 95% confidence interval [CI], 0.82–1.10; $P = 0.50$).

The APROCCHSS[6] trial included patients who were experiencing more severe shock and on higher doses of vasopressors compared to ADRENAL. The study compared hydrocortisone 50 mg IV bolus every 6 h plus fludrocortisone 50 mcg tablet daily to placebo for 7 days. The trial included 1241 patients from 34 French ICUs between September 2008 and June 2015. The trial found that 264 of 614 (43%) patients died by day 90 in the intervention group compared to 308 of 627 (49.1%) patients in the control group (relative risk 0.88, 95% CI 0.78–0.99; $P = 0.03$). Both ADRENAL and APROCCHSS trials showed reduction in vasopressor use and mechanical ventilation duration and length of stay.

Respiratory

The use of extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome (ARDS) has been studied since 1979 with two earlier trials did not show significant improvement, but both trials suffered technical difficulties as the technology was fairly primitive then.[7,8] The CESAR trial showed that referral to an ECMO center for consideration for ECMO improved outcomes. However, many patients in the ECMO arm did not receive ECMO, and the treatments in the control arm were not standardized.[9]

The latest study EOLIA[10] RCT compared early venovenous ECMO to

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Table 1: Major 2018 randomized controlled trials in the critical care

Study	PICO (Patients, intervention, comparison and outcome) questions
Steroids	
ADRENAL	In critically ill patients with septic shock, does hydrocortisone compared with placebo reduce 90-day mortality?
APROCCHSS	In critically ill patients with septic shock, does the combination of hydrocortisone plus fludrocortisone therapy reduce 90-day mortality?
Respiratory	
EOLIA	In patients with severe ARDS, does the early initiation of ECMO, compared to standard care, improve 60-day mortality?
HIGH	In immunocompromised patients with acute hypoxemic respiratory failure, does the use of high-flow oxygen, compared with standard oxygen therapy, reduce 28-day mortality?
BREATH	In adult patients on invasive mechanical ventilation who are difficult to wean, does extubation to NIV compared to weaning on invasive ventilation reduce the time to liberation from mechanical ventilation?
PREVENT	In mechanically ventilated patients without ARDS, does a low-tidal volume ventilation strategy (6 mL/kg), compared to intermediate-tidal volume strategy (10 mL/kg), reduce the number of ventilator-free and alive days at day 28?
Renal/fluid	
SMART	In critically ill patients, does the administration of balanced crystalloids, compared with saline, reduce 30-day composite outcome of death, new RRT or persistent renal dysfunction?
SALT-ED	In noncritically ill adult patients admitted to hospital from the emergency department, does the administration of a balanced salt crystalloids, compared with saline with normal saline, reduce hospital-free days to day 28?
BICAR-ICU	In critically ill patients with severe metabolic acidemia (pH $\leq$7.20), does the infusion of sodium bicarbonate, compared with no infusion, to reach and maintain a targeted pH of 7.30 decrease the primary composite outcome of mortality by day 28 or the presence of at least one organ failure at day 7?
IDEAL-ICU	In patients with septic shock and severe acute kidney injury, does early vs. delayed RRT improve 90-day mortality?
Ulcer prophylaxis/nutrition	
TARGET	In mechanically ventilated, critically ill patients receiving enteral nutrition does energy-dense feed (1.5 kCal/ml), compared with routine feed (1 kCal/ml), impact on 90-day all-cause mortality?
SUP-ICU	In ICU patients at risk of GI bleeding, does the use of prophylactic PPI, compared to placebo, reduce mortality at 90 days?
NUTRIREA-2	In mechanically ventilated, critically ill patients on catecholamines dose, does early nutrition via the enteral route route, compared to early intravenous feeding, reduce 28-day mortality?
Neurologic/psychologic	
POLAR	In patients with severe blunt TBI, does early and sustained cooling, compared with standard care, improve neurological outcomes at 6 months?
MIND-USA	In delirious adult ICU patients, does the administration of haloperidol or ziprasidone reduce the duration of delirium when compared with placebo?
PARTNER	For surrogate decision makers of critically ill patients, does a multi-component family support intervention impact the surrogates' HADS at 6 months?

ECMO=Extracorporeal membrane oxygenation, ARDS=Acute respiratory distress syndrome, PPI=Proton-pump inhibitor, GI=Gastrointestinal, HADS=Hospital anxiety and depression scale, ICU=Intensive Care Unit, NIV=Noninvasive ventilation, RRT=Renal replacement therapy, TBI=Traumatic brain injury

volume-assist-controlled ventilation in 249 patients with ARDS. The study was conducted in 64 centers, predominantly in France. Non-ECMO centers were included if they had extensive expertise in treating patients with ARDS and ECMO could be established within 2 h of randomization. The trial found that ECMO for severe ARDS had no significant benefit of mortality at day 60 as compared with a strategy of conventional MV, which included crossover to ECMO (Relative risk, 0.76; 95% CI, 0.55–1.04; P = 0.09). However, despite the lack of statistical significance, the data did not exclude the possibility of clinical benefit from ECMO over standard care.

The BREATH[11] trial compared early extubation to noninvasive ventilation (NIV) to standard weaning procedure from mechanical ventilation. The study was conducted in 41 general adult ICUs across the United Kingdom from March 2013 to October 2016 and included 364 patients who failed a spontaneous breathing trial. The study found that early extubation to NIV did not reduce the time to complete liberation from MV (median

time to liberation from ventilation was 4.3 days [95%CI, 2.63–5.58 days] in the noninvasive group and 4.5 days [95%CI, 3.46–7.25 days] in the invasive group).

The FLORALI trial[12] found that the use of high-flow nasal oxygen compared to other oxygen delivery methods in a broadly defined group of patients with acute hypoxemic respiratory failure improved ICU and 90-day mortality. The HIGH trial[13] addressed whether high-flow nasal oxygen improves outcomes of immunocompromised patients with acute hypoxemic respiratory failure. The study was conducted in 32 French hospitals and included 778 patients who were randomized to high-flow nasal oxygen versus normal oxygen delivery. The study found that high-flow nasal oxygen did not decrease 28-day mortality compared to standard oxygen (hazards ratio, 0.98 [95% CI, 0.77–1.24], $P = 0.94$).

The current clinical practice guidelines recommend using low tidal volumes (6 mL/kg) during mechanical ventilation of patients with ARDS.[14] It is less certain whether tidal volume restriction would benefit patients without ARDS. The PREVENT[15] trial compared low tidal volume (6 ml/kg predicted body weight (PBW) to intermediate tidal volume (10 mL/kg PBW) strategies in 961 adults non-ARDS patients. The study found that ventilation strategy using low tidal volume was not more effective than a strategy using intermediate tidal volume with respect to the number of ventilator-free days and alive at day 28 (mean difference, −0.27 [95% CI−1.74-1.19]; $P = 0.71$).

Renal/Fluid

Normal saline (0.9% sodium chloride) is the most commonly used crystalloid, but its safety has been questioned, as its administration in large quantities can cause hyperchloremic acidosis and may reduce renal blood flow and lead to worsening in kidney function. Two large randomized trials, the SMART[16] (15,802 patients) and the SALTED-ED[17] (13,347 patients) compared balanced crystalloids (lactated Ringer's and Plasma-Lyte) to saline in critically ill[16] and noncritically ill adults,[17] respectively. The SMART study showed that administering intravenous balanced crystalloids compared to saline reduced a composite outcome of death, new renal replacement therapy (RRT) or persistent renal dysfunction at 30 days (Conditional OR, 0.90; 95% CI, 0.82–0.99; $P = 0.04$). SALTED-ED study showed that the primary outcome of the number of hospital-free days did not differ between patients assigned to balanced crystalloids and those assigned to saline (median, 25 days in each group; adjusted OR with balanced crystalloids, 0.98; 95% CI, 0.92–1.04; $P = 0.41$), although patients in the balanced crystalloids group had a significantly lower incidence of major adverse kidney events within 30 days (MAKE 30) than those in the saline group (4.7% vs. 5.6%; adjusted OR, 0.82; 95% CI, 0.70–0.95; $P = 0.01$).

The BICAR-ICU[18] study was a multicenter, open-label, RCT conducted in 26 French ICUs and included 389 patients. The trial examined whether the infusion of sodium bicarbonate in patients with severe metabolic acidemia, compared with no infusion, to reach and maintain a targeted pH of 7.30 would decrease the primary composite outcome of mortality by day 28 or the presence of at least one organ failure at day 7. The study showed that sodium bicarbonate had no effect on the primary composite outcome (absolute difference estimate – 5.5%, 95% CI – 15.2–4.2; $P = 0.24$). However, sodium bicarbonate decreased the primary composite outcome and day 28 mortality in the a-priori defined stratum of patients with acute kidney injury (74/90 [82%] in the control group vs. 64/92 [70%] in the bicarbonate group; $P = 0.046$) and decreased day 28 mortality (57/90 [63%] in the control group vs. 42/92 [46]) in the bicarbonate group; $P = 0.0166$).

Acute kidney injury is a common occurrence in patients with septic shock. The decision as to when to start RRT is controversial. The AKIKI[19] trial reported no difference in mortality with an early versus a delayed approach, whereas the ELAIN[20] trial found a significant mortality benefit with the early approach. The more recent trial IDEAL-ICU[21] was conducted in 29 ICUs in France and included 488 patients with early-stage septic shock who had severe acute kidney injury. Patients were randomized to early initiation of RRT within 12 h of documentation of "failure-stage" acute kidney injury or to deferred initiation of RRT to 48 h postdiagnosis of "failure-stage" of acute kidney injury if the renal function had not spontaneously recovered or criteria for emergency RRT had been met. The study showed no difference in all-cause 90-day mortality with early compared with a late strategy for RRT (58% in early strategy vs. 54% in delayed strategy, $P = 0.38$).

Ulcer Prophylaxis/Nutrition

The benefit of proton pump inhibitors (PPIs) for stress ulcer prophylaxis has recently been questioned. The SUP-ICU[22] study compared prophylactic PPI to placebo in ICU patients at risk of gastrointestinal bleeding. The study was conducted in 33 ICUs in 6 countries and included 3298 patients. The study showed no significant differences between pantoprazole and placebo in 90-day mortality (relative risk, 1.02; 95% CI 0.91–1.13; $P = 0.76$). Clinically important GI bleeding occurred in 2.5% of patients in the pantoprazole group compared to 4.2% of patients in the control group (absolute risk reduction 1.7, CI 0.47–2.92, $P = 0.009$, number needed to treat 59).

Whether the route of early feeding with enteral compared to parenteral nutrition affects outcomes of patients with severe critical illness is controversial. The NUTRIREA-2[23] trial was conducted in 44 French ICUs and included 2410 patients who were receiving invasive mechanical ventilation and vasopressor support for shock. Patients were randomized within 24 h after intubation to receive parenteral nutrition or enteral nutrition, both targeting normocaloric goals (20–25 kcal/kg per day). The results showed that early enteral nutrition and early parenteral nutrition did not differ with regard to the primary outcome of 28-day mortality (absolute difference estimate 2.0% [95% CI – 1.9–5.8]; $P = 0.33$). However, early enteral nutrition was associated with an increase in the occurrence of ischemic bowel (hazards ratio 3.84 , 95% CI 1.43–10.3, $P = 0.007$), and colonic pseudo-obstruction (hazards ratio 3.7, 95% CI 1.03–13.2, $P = 0.04$).

The TARGET[24] trial compared between energy-dense feeding (1.5kCal/ml) and routine feeding (1kCal/ml) in mechanically ventilated, critically ill patients. The study was conducted in 46 ICUs in Australia and New Zealand and included 3914 patients. The study showed that energy-dense enteral nutrition did not improve 90-day survival amongst ventilated ICU patients (relative risk 1.05; 95% CI, 0.94–1.16, $P = 0.41$).

Neurologic/Psychologic

The induction of hypothermia in patients with traumatic brain injury was shown to improve outcomes in small clinical studies; however, two RCTs with a total of 768 patients failed to show better outcomes in patients with severe brain injury treated with hypothermia.[25,26] The POLAR[27] trial was conducted in 14 institutes in 6 countries (Australia, France, Saudi Arabia, Qatar, Switzerland, and New Zealand) and included 510 patients who were randomized to hypothermia protocol with a target temperature of 35°C compared to normothermia protocol with a temperature target of 36.5°C–37.5°C. The proportion of patients with favorable neurological outcomes (Glasgow Outcome Score Extended: GOSE 5–8) at 6 months' following injury was not statistically significant between the hypothermia group compared the normothermia group (relative risk, 0.99 [95% CI, 0.82–1.19]; $P = 0.94$).

Multidisciplinary support of families during crisis is a logical and inexpensive approach to communication, but data are lacking as to how effective it is. The PARTNER trial[28] was performed in 5 ICUs and enrolled 1420 patients. A nurse who received advanced communication training met with the family/surrogate on a daily basis and arranged a clinician-family meeting within 48 h of admission and every 5–7 days thereafter. A quality-improvement specialist incorporated the family-support pathway into the clinician's workflow. The study showed that the family-support intervention did not affect the surrogates' symptoms of depression and anxiety at 6 months (Estimated effect of intervention: 0.34, 95% CI - 1.67–0.99; $P = 0.61$). However, the surrogates' ratings of the quality of communication and the patient- and family-centeredness of care were better, and the length of stay in ICU was shorter with the intervention compared with usual care.

Delirium is the most common manifestation of acute brain dysfunction during critical illness. Trials using haloperidol and atypical antipsychotic medications have failed to show a clear benefit in the management of delirium.[29] the MIND-USA[30] study revisited this issue by randomizing 566 patients to receive placebo, haloperidol or ziprasidone in a 1:1:1 ratio. The study found no evidence that the use of haloperidol or ziprasidone had an effect on the number of days alive without delirium or coma during the 14-day intervention period among patients with acute respiratory illness or shock in the ICU (adjusted median number of days alive and without delirium or coma was 8.5 (95% CI 5.6–9.9) in the placebo group, 7.9 (95% CI 4.4–9.6) in the haloperidol group, 8.7 (95% CI 5.9–10.0) in the ziprasidone group (P value across trial groups = 0.26).

Conclusion

There were several major clinical trials published in 2018 addressing highly relevant questions in critical care. These trials are expected to be incorporated into clinical practice guidelines.

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Conflicts of interest
There are no conflicts of interest.

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