Which Multicenter Randomized Controlled Trials in Critical Care Medicine Have Shown Reduced Mortality? A Systematic Review

Carlos A. Santacruz, MD[1]; Adriano J. Pereira, MD, PhD[2]; Edgar Celis, MD[1]; Jean-Louis Vincent, MD, PhD, FCCM[3]

Objectives: To determine which multicenter randomized controlled trials in critically ill patients have shown that the study intervention was associated with a statistically significant reduction in mortality. Our analysis provides an update to a report published 10 years ago.

Data Sources: MEDLINE database and PubMed interface from inception until April 30, 2019.

Study Selection: All adult multicenter randomized controlled trials that evaluated the effects of any intervention or monitoring system in critically ill patients and reported mortality as a primary or secondary outcome were included.

Data Extraction: Numbers of centers and patients, type of intervention, reported mortality outcome, and rate and level of significance were extracted into predefined tables. Included randomized controlled trials were classified as reporting reduced, increased, or no effect of the intervention on mortality. Methodologic quality of trials was evaluated using the updated Consolidated Standards of Reporting Trials statement.

Data Synthesis: A total of 212 trials met the inclusion criteria: 27 (13%) reported a significant reduction in mortality, 16 (7%) an increase in mortality, and 170 (80%) no difference in mortality (one study was reported in 2 groups). Of the 27 trials reporting reduced mortality, six had assessed interventions likely to decrease ventilator-induced lung injury, including low tidal volume, prone position, and neuromuscular blockers, demonstrating the negative effects of mechanical ventilation strategies or improved process of care rather than positive effects of new therapies. Seven of the 27 trials reported beneficial effects of noninvasive ventilation. Results from some positive randomized controlled trials, for example, studies of recombinant activated protein C, talactoferrin, interleukin-1 receptor antagonist in sepsis, and muscle relaxants in severe acute respiratory distress syndrome were not replicated in subsequent randomized controlled trials. Other interventions, for example, gastric tonometry, have been abandoned.

Conclusions: A systematic literature search provided no conclusive evidence of any pharmacologic intervention that has consistently reduced mortality in critically ill patients. Strategies associated with improved or noninvasive mechanical ventilation were associated with reduced mortality. (*Crit Care Med* 2019; 47:1680–1691)

Key Words: critically ill; heterogeneity; iatrogenicity; outcomes; process of care

[1]Department of Critical and Intensive Care Medicine, Academic Hospital Fundación Santa Fe de Bogotá, Bogotá, Colombia.

[2]Department of Intensive Care, Hospital Israelita Albert Einstein, Sao Paolo, Brazil.

[3]Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium.

Drs. Santacruz and Vincent designed the study. Drs. Santacruz and Pereira performed the literature search and extracted the data. Dr. Santacruz wrote the first draft of the article. Drs. Pereira, Celis, and Vincent reviewed the article for critical content. All authors read and approved the final text.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: jlvincent@intensive.org

DOI: 10.1097/CCM.0000000000004000

Randomized controlled trials (RCTs) are considered the best evidence to guide clinical practice because the randomization process can control for unmeasurable factors that may influence the response to a therapeutic intervention (1). In critical care medicine, mortality is often chosen as the main outcome measure for clinical trials because it is dichotomous, clinically relevant, and relatively high in critically ill patients. However, many factors, in addition to a patient's current disease process, can influence survival, including availability and choice of therapy and personal preferences about end-of-life decisions (2). Biological heterogeneity, including variation in age, sex, genetics/genomics, physiologic response, immunophenotype, and comorbidities, among many others, will also influence the effect of any intervention on mortality (3). Hence, many large RCTs in critically ill patients targeting mortality as an outcome endpoint

have reported no overall effect of the intervention, that is, have been reported as "negative."

Ten years ago, we performed a systematic review of the literature to determine which RCTs evaluating interventions in critically ill patients had reported statistically significantly reduced mortality rates in the intervention arm (4). The results showed that only 10 of the 72 studies (14%) included in the review had shown a beneficial impact of the intervention on survival of critically ill patients. Given the large number of RCTs that have been published in the intervening period and increased recognition of the problems with conducting RCTs in ICU patients (5), we decided to update this analysis.

MATERIALS AND METHODS

We conducted a systematic search of the literature from inception up to April 30, 2019, using the MEDLINE database and the PubMed interface, to identify multicenter RCTs that had evaluated any pharmacologic or mechanical intervention or monitoring system in adult critically ill ICU patients and had reported mortality as a predefined primary or secondary outcome.

We used the mesh terms: ((((((((((("critical care"[MeSH Terms] OR "critical care"[Text Word]) OR "intensive care"[Text Word]) OR ("critical illness"[MeSH Terms] OR "critical illness"[Text Word])) OR "critically ill"[Text Word]) OR ("sepsis"[MeSH Terms] OR "sepsis"[Text Word])) OR ("respiration, artificial"[MeSH Terms] OR "artificial respiration"[Text Word])) OR "mechanical ventilation"[Text Word]) OR ("respiratory distress syndrome, adult"[MeSH Terms] OR "adult respiratory distress syndrome"[Text Word])) OR ("cardiopulmonary resuscitation"[MeSH Terms] OR "cardiopulmonary resuscitation"[Text Word])) OR ("heart arrest"[MeSH Terms] OR "cardiac arrest"[Text Word])) OR "ards"[Text Word] AND ((Randomized Controlled Trial[ptyp] OR Multicenter Study[ptyp]) AND "Mortality"[Mesh]. Limits: Humans, Clinical trials, Adults +19. We excluded trials that were not multicenter and not randomized, trials involving only pediatric or non-ICU populations or in which the intervention was conducted prior to ICU admission and those in which mortality was not mentioned as an outcome. No date limit or minimum number of patients was applied. Only English-language articles were included. We also searched the references of included articles and related review articles for studies that had been missed in the initial search.

Eligibility assessment and data abstraction, including numbers of centers and patients, type of intervention, type of mortality outcome and rate as well as the level of significance was performed by two reviewers (C.A.S., A.J.P.) who completed predefined tables independently in a blinded manner. RCTs were classified as reporting statistically significantly reduced, increased, or no effect of the intervention on mortality. All results were included regardless of the test used to evaluate statistical significance. Discrepancies in the final classification of the RCTs were resolved by consensus among all authors.

Median (interquartile range [IQR] 25–75%) mortality, number of participating centers, and total number of included subjects are reported for each category. Trials were subgrouped according to most frequent populations into "sepsis" (including vasodilatory and distributive shock), "acute respiratory distress syndrome [ARDS]/acute lung injury," "acute respiratory failure" (hypercapnic and hypoxemic respiratory failure), and "general ICU." Trials that reported survival rates were excluded from the overall mortality analysis. The Wilcoxon signed rank test was used to compare the median (IQR) of predicted and observed mortality for the control groups of all RCTs in the three categories. Statistical analyses were performed using the latest version of R program (6).

Trial methodologic quality was assessed by evaluating reports of blinding, use of intention-to-treat analysis, and allocation generation and concealment, according to the directions of the updated Consolidated Standards of Reporting Trials statement (7). Concealment was considered adequate if the author reported a mechanism used to implement the random allocation sequence, describing any steps taken to conceal the sequence until interventions were assigned. We classified the type of analysis (intention to treat or per protocol) as adequate if all randomized patients were included in the analysis in the original group to which they had been allocated. Sample size calculation was not reported in trials where mortality was not the primary outcome.

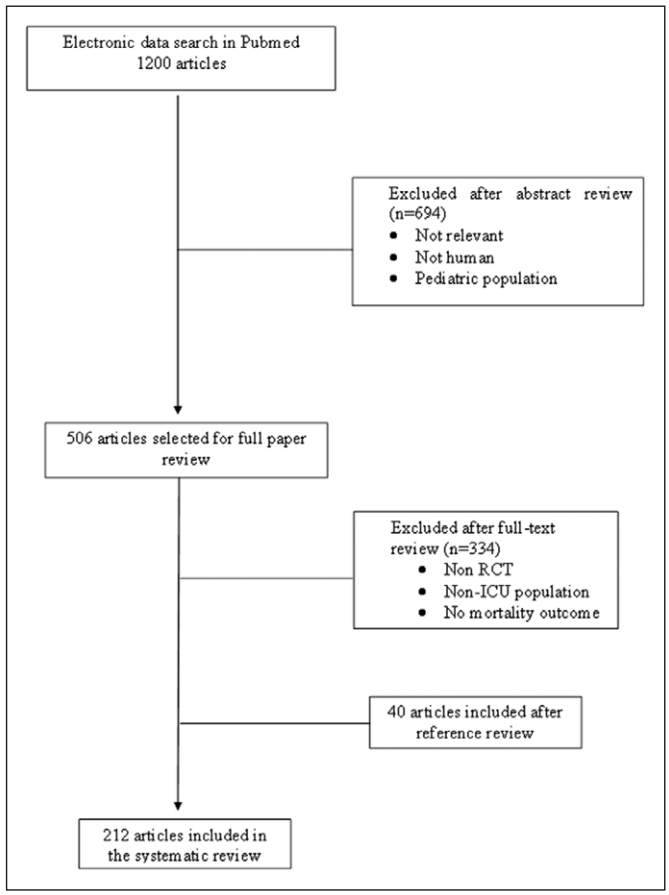

Figure 1. Flow chart of included trials. RCT = randomized controlled trial.

TABLE 1. Randomized Controlled Trials in Which Decreased Mortality Was Reported (Full Study Details in Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/E922)

References	Study Population	Intervention	
		Study Group	Control Group
Amendola et al (8)	Acute kidney injury	Goal-directed therapy	Standard practice
Annane et al (9)	Sepsis	Hydrocortisone + fludrocortisone	Placebo
de Jong et al (10)	ICU	Procalcitonin-guided therapy	Standard practice
Guérin et al (11)	ARDS	Prone position	Supine position
Guntupalli et al (12)	Sepsis	Talactoferrin	Placebo
Nava et al (13)	AHRF	NIV	Standard practice
Papazian et al (14)	ARDS	Cisatracurium besylate	Placebo
Ferrer et al (15)	AHRF	NIV	Conventional oxygen
de Smet et al (16)	ICU	Selective digestive decontamination/ selective oral decontamination	Standard practice
Ferrer et al (17)	ICU	NIV	Conventional oxygen
Villar et al (18)	ARDS	Pflex/low V_T	Standard practice
Panacek et al (19)	Sepsis	Afelimomab	Placebo
Ferrer et al (20)	ICU	NIV during weaning	Conventional weaning
Ferrer et al (21)	Acute hypoxemic respiratory failure	NIV	High-concentration oxygen
Annane et al (22)	Sepsis	Hydrocortisone + fludrocortisone	Placebo
Bernard et al (23)	Sepsis	Recombinant human activated protein C	Placebo
Brower et al (24)	ARDS	V_T 6 mL/kg PBW	V_T 12 mL/kg PBW
Esteban et al (25)	ARDS	Pressure-controlled ventilation	Volume-controlled ventilation
Fagon et al (26)	Pneumonia	Invasive management in ventilator-associated pneumonia	Clinical management
Nava et al (27)	AHRF	Noninvasive pressure support ventilation	Invasive pressure support ventilation
Amato et al (28)	ARDS	Protective ventilation	Conventional ventilation
Baudo et al (29)	Sepsis	Antithrombin III	Placebo
Brochard et al (30)	AHRF	NIV	Standard practice
Fisher et al (31)	Sepsis	Interleukin-1 receptor antagonist	Placebo
Gutierrez et al (32)	ICU	Gastric intramucosal pH	Standard practice
Dominioni et al (33)	Sepsis	High dose immunoglobulin G	Placebo
Ziegler et al (34)	Sepsis and gram-negative bacteremia	Human monoclonal immunoglobulin M antibody	Placebo

AHRF = acute hypercapnic respiratory failure, ARDS = acute respiratory distress syndrome, NIV = noninvasive ventilation, PBW = predicted body weight, V_T = tidal volume.

RESULTS

A total of 1,200 articles were identified in the initial search and 40 after reference review; 212 RCTs met the inclusion criteria (**Fig. 1**). Of the 212 RCTs, 27 reported reduced mortality (8–34) (**Table 1**; and **Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/E922), 16 increased mortality (25, 35–49) (**Table 2**; and **Table S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/E922), and 170 no effect on mortality (50–219) (**Table S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/E922). One study (25) that showed

TABLE 2. Randomized Controlled Trials in Which Increased Mortality Was Reported (Full Study Details in Table S2, Supplemental Digital Content 1, http://links.lww.com/CCM/E922)

References	Study Population	Intervention	
		Study Group	Control Group
Guidet et al (35)	ICU	Systematic ICU admission	Standard practice
Cavalcanti et al (36)	ARDS	Recruitment maneuver and PEEP titration	Low PEEP
Ferguson et al (37)	ARDS	High-frequency oscillatory ventilation	Pressure-controlled ventilation
Heyland et al (38)	ICU	Glutamine, antioxidants, or both	Placebo
Mourvillier et al (39)	Sepsis	Hypothermia	Standard practice
Perner et al (40)	Sepsis	6% hydroxyethyl starch 130/0.42	Ringer´s acetate
Gao Smith et al (41)	ARDS	IV salbutamol	Placebo
Elseviers et al (42)	Acute kidney injury	Renal replacement therapy	Conservative management
López et al (43)	Sepsis	Nitric oxide synthase inhibitor 546C88	Placebo
Esteban et al (44)	Acute respiratory failure	Noninvasive positive pressure ventilation	Standard practice
Mehta et al (45)	ICU	Continuous renal replacement therapy	Intermittent hemodialysis
Esteban et al (25)	ARDS	Volume-controlled ventilation	Pressure-controlled ventilation
Sloan et al (46)	Hemorrhagic shock	Diaspirin cross-linked hemoglobin	Placebo
Takala et al (47)	ICU	Growth hormone	Placebo
Fisher et al (48)	Sepsis	Tumor necrosis factor receptor and Fc portion of immunoglobulin G1	Placebo
Hayes et al (49)	ICU	High Do_2 and Vo_2	Normal Do_2 and Vo_2

ARDS = acute respiratory distress syndrome, Do_2 = oxygen delivery, PEEP = positive end-expiratory pressure, Vo_2 = oxygen consumption.

a difference in mortality was included in both the increased and decreased mortality groups because the interventions were at equipoise so neither could be considered as a standard control or placebo. Hence the results showed an increase or decrease in mortality depending on which group was taken as comparator.

RCTs Reporting Reduced Mortality

Twenty-seven RCTs in a total of 15,612 patients from a median of 10 (3–22) centers reported reduced mortality (or increased survival) with the intervention under study. Four studies in this category reported survival rates (20, 22, 27, 29) and were not included in the mortality analyses. The median (IQR) mortality in the remaining 23 studies was 25.7% (16.7–31.8%) in the intervention group versus 41.9% (30.9–49.9%) in the control group (n = 23 studies). Seven studies were conducted in patients with sepsis (n = 4,480, median mortality 30.0% [24.5–40.5%] intervention vs 47.6% [39.8–49.1%] control) (9, 12, 19, 23, 31, 33, 34). Other frequently studied populations included patients with ARDS (six studies, n = 1,894, mortality 31.5% [30.9–36.5%] vs 49.0% [41.0–66.6%]) (11, 14, 18, 24, 25, 28) and patients with acute hypercapnic or hypoxemic respiratory failure (four studies, n = 377, mortality 10.9% [9.8–13.3%] vs 35.0% [30.5–41.8%]) (13, 15, 21, 30).

The six studies in patients with ARDS evaluated strategies that would reduce ventilator-induced lung injury, assessing a low tidal volume ventilation strategy associated with a high positive end-expiratory pressure (18, 24, 28), pressure versus volume cycle controlled mechanical ventilation (25), prone positioning (11), and IV administration of cisatracurium besylate (14). Seven studies had evaluated use of noninvasive ventilation (NIV) in patients with acute hypercapnic respiratory failure (AHRF) or when weaning from mechanical ventilation in general ICU patients (13, 15, 17, 20, 21, 27, 30). The other 14 trials had evaluated anti-inflammatory or immunomodulatory therapies in patients with sepsis or bacteremia (9, 12, 19, 22, 23, 29, 31, 33, 34), procalcitonin-guided antibiotic therapy (10), digestive decontamination (16), diagnostic strategies for ventilator-associated pneumonia (26), goal-directed therapy in patients with acute kidney injury (8), and hemodynamic optimization monitoring using gastric tonometry (32) (Table 1; and Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/E922).

RCTs Reporting Increased Mortality

Sixteen RCTs in a total of 10,462 patients from a median of 25 (14–42) centers reported increased mortality with the intervention under study (25, 35–49). One study in this category (43)

reported survival rates and was not included in the mortality analyses. The median mortality in the remaining 15 studies was 50.3% (43.3–53.5%) for the intervention group versus 34.0% (24.1–42.3%) in the control group. Five studies were conducted in general ICU populations (n = 5,043, mortality 45.0% [41.5–54.0%] vs 34.0% [27.2–39.0%]) (35, 38, 45, 47, 49). Other groups frequently studied included patients with ARDS (four studies, n = 1,963, mortality 51.2% [43.8–61.0%] vs 42.2% [32.0–49.7%]) (25, 36, 37, 41) and patients with sepsis (three studies, n = 1,037, mortality 51.0% [51.0–52.0%] vs 34.0% [32.0–38.5%]) (39, 40, 48) (Table 2; and Table S2, Supplemental Digital Content 1, http://links.lww.com/CCM/E922).

RCTs Showing No Effect on Mortality

In 170 RCTs, in a total of 145,662 patients from a median of 26 (11–55) centers, no statistically significant effect of the intervention under study on mortality was reported (Table S3, Supplemental Digital Content 1, http://links.lww.com/CCM/E922). Nine studies in this category (57, 70, 83, 90, 93, 125, 171, 178, 190) reported survival rates and were not included in the mortality analyses. The median mortality in the remaining 161 studies was 29.0% (21.0–37.0%) for the intervention group versus 30.0% (24.0–38.0%) for the control group. Sixty-five studies were conducted in patients with sepsis (n = 52,005, mortality 30% [26–39%] vs 32% [26–39%]). Other frequently studied groups included general ICU populations (31 studies, n = 58,068, mortality 29.0% [21.0–33.5%] vs 28.0% [22.0–33.0%]) and patients with ARDS (23 studies, n = 9,814, mortality 31.0% [28.5–39.0%] vs 34.0% [28.0–43.5%]). The most recent RCTs to report no effect on mortality were studies assessing the use of lactate levels to guide resuscitation in sepsis (50), probiotics to prevent ventilator-associated pneumonia (51), adjunctive intermittent pneumatic compression to prevent deep-vein thrombosis (52), and levocarnitine in patients with sepsis (53).

Methodologic Quality of Included Trials

Allocation concealment was reported in 25 of the 27 trials (93%) with reduced mortality rates, in 11 of the 16 (69%) with increased mortality and in 148 of 170 neutral trials (87%) (**Tables S4–S6**, Supplemental Digital Content 1, http://links.lww.com/CCM/E922). Intention to treat or modified intention to treat analyses were reported as having been carried out in 22 of 27 trials (81%) in the reduced mortality group, in 13 of 16 trials (81%) in the increased mortality group, and in 158 of 170 (93%) of the neutral trials group.

There was no statistically significant difference between the control group median assumed and observed mortality rates in the RCTs reporting reduced mortality (45.0% [30.0–50.0%] vs 39.8% [30.2–49.1%]; p = 0.66), increased mortality (35.0% [33.0–34.0%] vs 34.0% [23.0–39.0%]; $p > 0.99$]), or no effect (40.0% [28.0–48.3%] vs 30.0% [24.0–38.3%]; p = 0.33).

DISCUSSION

This systematic review shows that only 13% of published RCTs demonstrated that the intervention being tested was associated with reduced mortality rates. These observations confirm and extend those of our earlier review 10 years ago (4) in which 14% of the included RCTs had shown a beneficial effect of the intervention on mortality rates. Importantly, it is well known that "negative" trials are less likely to be published than those with significant differences between study arms (220), so the actual percentage of total trials conducted that demonstrate a beneficial effect on survival is likely to be much less than the 13% we identified in published RCTs.

Importantly, many of the RCTs that showed a decrease in mortality studied interventions that reduced iatrogenic conditions, notably in patients with ARDS (11, 14, 18, 24, 25, 28), rather than demonstrating an effect of a new therapy on mortality. The only intervention consistently shown to improve outcomes was use of NIV in patients with AHRF or when weaning from invasive mechanical ventilation (13, 15, 17, 20, 21, 27, 30). For several of the RCTs that reported a decrease in mortality (12, 14, 23), the findings were not replicated in later larger studies (e.g., recombinant activated protein C [121], talactoferrin [97], and neuromuscular blockade in severe ARDS [221]), or, as for gastric tonometry (32), the interventions have been abandoned. In **Table 3**, we present a simple overview of the current status of the interventions shown by RCT to reduce mortality in ICU patients.

There are multiple reasons why an RCT may not demonstrate a difference between intervention arms apart from the obvious possibility that the intervention is not effective. Notably, lower overall mortality rates in ICU patients in recent years may make it more difficult to detect a mortality difference with any intervention. For example, the control groups of recent studies of early goal-directed therapy in ICU patients had mortality rates of ± 25% (98–100) compared with the initial study by Rivers et al (222) in which mortality was 46% in the control group.

Another key reason for the many studies that report no effect of an intervention is the heterogeneity of the patients included. Despite broad clinical and biological heterogeneity in study groups, particularly in patients with sepsis and ARDS, most studies still report an "average" treatment effect, which assumes that the effect of treatment would have been the same in all patients. The heterogeneity of treatment effect is examined primarily by subgroup analyses, some of which have indeed shown decreased mortality in RCTs in which the overall outcome effect was negative. For example, Ziegler et al (34) reported no overall effect of human monoclonal antibody against endotoxin in patients with presumed Gram-negative sepsis, but reduced mortality in patients with proven Gram-negative bacteremia. And Bone et al (218) reported no overall difference in 14-day mortality in patients with sepsis treated with high dose methylprednisolone, but a significant decrease in mortality in a subgroup of patients with elevated serum creatinine levels. Nevertheless, subgroup analyses have reduced power compared with analyses involving the full study cohort and must be interpreted with some caution.

Several approaches to study design have been suggested to overcome the problem of heterogeneity. Performing larger RCTs may increase the credibility of subgroup analysis, but enrolling more patients prolongs study duration and costs. Alternatively, adaptive design RCTs (223–225) have been proposed to try and improve the likelihood of detecting a difference between study arms. Such studies adapt the study design while the study is in

TABLE 3. A Simple Overview of the Current Status of the Interventions Shown by Randomized Controlled Trial to Reduce Mortality in ICU Patients

Type of Intervention	Well Accepted	Still Debated[a]	Largely Unaccepted/ Disproved
Limiting iatrogenicity/respiratory support			
Limited tidal volume in ARDS	X		
NIV in hypercapnic respiratory failure	X		
NIV following extubation in complex cases	X		
Prone positioning in severe ARDS		X	
Muscle relaxants in severe ARDS			X
Monitoring systems			
Gastric tonometry			X
New therapeutic interventions			
Interleukin-1 receptor antagonist in sepsis			X
Drotrecogin alfa (activated) in sepsis			X
Talactoferrin in sepsis			X
Polymyxin B hemoperfusion in sepsis			X
Other strategies			
Selective digestive decontamination		X	
Corticosteroids in septic shock		X	
Early goal-directed therapy in acute kidney injury		X	

ARDS = acute respiratory distress syndrome, NIV = noninvasive ventilation.
[a]Perhaps applicable in some patients, but not for routine use.

progress, either by halting recruitment to study arms in which no benefit is shown at interim analysis, thus focusing the rest of the study on those arms most likely to demonstrate reduced mortality, or by recalculating sample sizes so that studies showing potential benefit, but which are underpowered can continue and ineffective interventions can be stopped early. However, such trials necessitate more complex statistical techniques (225). Alternatively, more careful patient characterization and selection is needed such that populations are more homogeneous and only patients most likely to respond to the intervention are included. This option will become increasingly possible as 'omics technology develops.

Finally, mortality may not be the best endpoint for RCTs in critically ill patients because it is difficult to influence outcomes, partly because mortality rates have decreased over time as mentioned earlier, but also because mortality is a heterogeneous outcome, which can be influenced by many factors beyond the intervention target, including patient end-of-life treatment preferences. Although patient survival is of course important, other patient-centered outcomes, such as improvement in organ function (226) or quality-of-life (227), should also be considered. Indeed, RCTs that report a reduction in mortality but have a high risk of bias may lead to excessive, potentially unnecessary interventions (8). Importantly, although the "at-a-glance" interpretation of so-called negative trials is that the intervention is not effective and should therefore not be used, RCTs with negative results in terms of mortality endpoints may still have important implications for daily ICU practice when other outcomes are considered, and results should still be published.

This review has several limitations. First is the simple classification we used to characterize study results, using a decrease, increase, or no effect on mortality, although there may be some subjectivity in the way in which study results are interpreted, and others may have classified some studies differently. Second, our search strategy was limited to the MEDLINE database, but we also carefully reviewed reference lists of the included articles and of relevant review articles and do not believe that important published RCTs escaped our search. Third, we did not study results of subgroup analyses as we were interested only in global study results. Finally, publication bias was not formally assessed.

CONCLUSIONS

Although 20% of studies have reported a statistically significant difference in survival, the large proportion of neutral trials suggests that careful thought is necessary when designing RCTs in terms of selection of patients and choice of outcomes. RCTs should target other outcomes than just mortality, and other study designs could also be considered.

REFERENCES

1. Vincent JL: Improved survival in critically ill patients: Are large RCTs more useful than personalized medicine? No. *Intensive Care Med* 2016; 42:1778–1780
2. Papadimos TJ, Maldonado Y, Tripathi RS, et al: An overview of end-of-life issues in the intensive care unit. *Int J Crit Illn Inj Sci* 2011; 1:138–146
3. Jensen HI, Ammentorp J, Ording H: Guidelines for withholding and withdrawing therapy in the ICU: Impact on decision-making process and interdisciplinary collaboration. *Heart Lung Vessel* 2013; 5:158–167
4. Ospina-Tascón GA, Büchele GL, Vincent JL: Multicenter, randomized, controlled trials evaluating mortality in intensive care: Doomed to fail? *Crit Care Med* 2008; 36:1311–1322
5. Vincent JL: We should abandon randomized controlled trials in the intensive care unit. *Crit Care Med* 2010; 38:S534–S538
6. R Core Team: A Language and Environment for Statistical Computing. Vienna, Austria, R Foundation for Statistical Computing. Available at: https://www.R-project.org/. Accessed September 5, 2019
7. Schulz KF, Altman DG, Moher D; CONSORT Group: CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340:c332
8. Amendola CP, Silva-Jr JM, Carvalho T, et al: Goal-directed therapy in patients with early acute kidney injury: A multicenter randomized controlled trial. *Clinics (Sao Paulo)* 2018; 73:e327
9. Annane D, Renault A, Brun-Buisson C, et al; CRICS-TRIGGERSEP Network: Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 2018; 378:809–818
10. de Jong E, van Oers JA, Beishuizen A, et al: Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: A randomised, controlled, open-label trial. *Lancet Infect Dis* 2016; 16:819–827
11. Guérin C, Reignier J, Richard JC, et al; PROSEVA Study Group: Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368:2159–2168
12. Guntupalli K, Dean N, Morris PE, et al; TLF LF-0801 Investigator Group: A phase 2 randomized, double-blind, placebo-controlled study of the safety and efficacy of talactoferrin in patients with severe sepsis. *Crit Care Med* 2013; 41:706–716
13. Nava S, Grassi M, Fanfulla F, et al: Non-invasive ventilation in elderly patients with acute hypercapnic respiratory failure: A randomised controlled trial. *Age Ageing* 2011; 40:444–450
14. Papazian L, Forel JM, Gacouin A, et al; ACURASYS Study Investigators: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363:1107–1116
15. Ferrer M, Sellarés J, Valencia M, et al: Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: Randomised controlled trial. *Lancet* 2009; 374:1082–1088
16. de Smet AM, Kluytmans JA, Cooper BS, et al: Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med* 2009; 360:20–31
17. Ferrer M, Valencia M, Nicolas JM, et al: Early noninvasive ventilation averts extubation failure in patients at risk: A randomized trial. *Am J Respir Crit Care Med* 2006; 173:164–170
18. Villar J, Kacmarek RM, Pérez-Méndez L, et al: A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: A randomized, controlled trial. *Crit Care Med* 2006; 34:1311–1318
19. Panacek EA, Marshall JC, Albertson TE, et al; Monoclonal Anti-TNF: a Randomized Controlled Sepsis Study Investigators: Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab')2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. *Crit Care Med* 2004; 32:2173–2182
20. Ferrer M, Esquinas A, Arancibia F, et al: Noninvasive ventilation during persistent weaning failure: A randomized controlled trial. *Am J Respir Crit Care Med* 2003; 168:70–76
21. Ferrer M, Esquinas A, Leon M, et al: Noninvasive ventilation in severe hypoxemic respiratory failure: A randomized clinical trial. *Am J Respir Crit Care Med* 2003; 168:1438–1444
22. Annane D, Sébille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862–871
23. Bernard GR, Vincent JL, Laterre PF, et al; Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699–709
24. Brower RG, Matthay MA, Morris A, et al; The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308
25. Esteban A, Alía I, Gordo F, et al: Prospective randomized trial comparing pressure-controlled ventilation and volume-controlled ventilation in ARDS. For the Spanish Lung Failure Collaborative Group. *Chest* 2000; 117:1690–1696
26. Fagon JY, Chastre J, Wolff M, et al: Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Ann Intern Med* 2000; 132:621–630
27. Nava S, Ambrosino N, Clini E, et al: Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. *Ann Intern Med* 1998; 128:721–728
28. Amato MB, Barbas CS, Medeiros DM, et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347–354
29. Baudo F, Caimi TM, de Cataldo F, et al: Antithrombin III (ATIII) replacement therapy in patients with sepsis and/or postsurgical complications: A controlled double-blind, randomized, multicenter study. *Intensive Care Med* 1998; 24:336–342
30. Brochard L, Mancebo J, Wysocki M, et al: Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; 333:817–822
31. Fisher CJ Jr, Slotman GJ, Opal SM, et al; IL-1RA Sepsis Syndrome Study Group: Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: A randomized, open-label, placebo-controlled multicenter trial. *Crit Care Med* 1994; 22:12–21
32. Gutierrez G, Palizas F, Doglio G, et al: Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 1992; 339:195–199
33. Dominioni L, Dionigi R, Zanello M, et al: Effects of high-dose IgG on survival of surgical patients with sepsis scores of 20 or greater. *Arch Surg* 1991; 126:236–240
34. Ziegler EJ, Fisher CJ Jr, Sprung CL, et al: Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. A randomized, double-blind, placebo-controlled trial. The HA-1A Sepsis Study Group. *N Engl J Med* 1991; 324:429–436
35. Guidet B, Leblanc G, Simon T, et al; ICE-CUB 2 Study Network: Effect of systematic intensive care unit triage on long-term mortality among critically ill elderly patients in France: A randomized clinical trial. *JAMA* 2017; 318:1450–1459
36. Cavalcanti AB, Suzumura EA, Laranjeira LN et al: Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: A randomized clinical trial. *JAMA* 2017; 318:1335–1345
37. Ferguson ND, Cook DJ, Guyatt GH, et al; OSCILLATE Trial Investigators; Canadian Critical Care Trials Group: High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013; 368:795–805
38. Heyland D, Muscedere J, Wischmeyer PE, et al; Canadian Critical Care Trials Group: A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med* 2013; 368:1489–1497
39. Mourvillier B, Tubach F, van de Beek D, et al: Induced hypothermia in severe bacterial meningitis: A randomized clinical trial. *JAMA* 2013; 310:2174–2183
40. Perner A, Haase N, Guttormsen AB, et al; 6S Trial Group; Scandinavian Critical Care Trials Group: Hydroxyethyl starch 130/0.42 versus ringer's acetate in severe sepsis. *N Engl J Med* 2012; 367:124–134
41. Gao Smith F, Perkins GD, Gates S, et al; BALTI-2 study investigators: Effect of intravenous β-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): A multicentre, randomised controlled trial. *Lancet* 2012; 379:229–235
42. Elseviers MM, Lins RL, Van der Niepen P, et al; SHARF investigators: Renal replacement therapy is an independent risk factor for mortality in critically ill patients with acute kidney injury. *Crit Care* 2010; 14:R221

43. López A, Lorente JA, Steingrub J, et al: Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: Effect on survival in patients with septic shock. *Crit Care Med* 2004; 32:21–30
44. Esteban A, Frutos-Vivar F, Ferguson ND, et al: Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med* 2004; 350:2452–2460
45. Mehta RL, McDonald B, Gabbai FB, et al; Collaborative Group for Treatment of ARF in the ICU: A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int* 2001; 60:1154–1163
46. Sloan EP, Koenigsberg M, Gens D, et al: Diaspirin cross-linked hemoglobin (DCLHb) in the treatment of severe traumatic hemorrhagic shock: A randomized controlled efficacy trial. *JAMA* 1999; 282:1857–1864
47. Takala J, Ruokonen E, Webster NR, et al: Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med* 1999; 341:785–792
48. Fisher CJ Jr, Agosti JM, Opal SM, et al: Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. The Soluble TNF Receptor Sepsis Study Group. *N Engl J Med* 1996; 334:1697–1702
49. Hayes MA, Timmins AC, Yau EH, et al: Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; 330:1717–1722
50. Hernández G, Ospina-Tascón GA, Damiani LP, et al; The ANDROMEDA SHOCK Investigators and the Latin America Intensive Care Network (LIVEN): Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: The ANDROMEDA-SHOCK randomized clinical trial. *JAMA* 2019; 321:654–664
51. Mahmoodpoor A, Hamishehkar H, Asghari R, et al: Effect of a probiotic preparation on ventilator-associated pneumonia in critically ill patients admitted to the intensive care unit: A prospective double-blind randomized controlled trial. *Nutr Clin Pract* 2019; 34:156–162
52. Arabi YM, Al-Hameed F, Burns KEA, et al; Saudi Critical Care Trials Group: Adjunctive intermittent pneumatic compression for venous thromboprophylaxis. *N Engl J Med* 2019; 380:1305–1315
53. Jones AE, Puskarich MA, Shapiro NI, et al: Effect of levocarnitine vs placebo as an adjunctive treatment for septic shock: The Rapid Administration of Carnitine in Sepsis (RACE) randomized clinical trial. *JAMA Netw Open* 2018; 1:e186076
54. Krag M, Marker S, Perner A, et al; SUP-ICU trial group: Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med* 2018; 379:2199–2208
55. Wittekamp BH, Plantinga NL, Cooper BS, et al: Decontamination strategies and bloodstream infections with antibiotic-resistant microorganisms in ventilated patients: A randomized clinical trial. *JAMA* 2018; 320:2087–2098
56. Pickkers P, Mehta RL, Murray PT, et al; STOP-AKI Investigators: Effect of human recombinant alkaline phosphatase on 7-day creatinine clearance in patients with sepsis-associated acute kidney injury: A randomized clinical trial. *JAMA* 2018; 320:1998–2009
57. Perkins GD, Mistry D, Gates S, et al; Breathe Collaborators: Effect of protocolized weaning with early extubation to noninvasive ventilation vs invasive weaning on time to liberation from mechanical ventilation among patients with respiratory failure: The breathe randomized clinical trial. *JAMA* 2018; 320:1881–1888
58. Azoulay E, Lemiale V, Mokart D, et al: Effect of high-flow nasal oxygen vs standard oxygen on 28-day mortality in immunocompromised patients with acute respiratory failure: The HIGH randomized clinical trial. *JAMA* 2018; 320:2099–2107
59. Nardi O, Zavala E, Martin C, et al: Targeting skeletal muscle tissue oxygenation (StO2) in adults with severe sepsis and septic shock: A randomised controlled trial (OTO-StS Study). *BMJ Open* 2018; 8:e017581
60. Itenov TS, Johansen ME, Bestle M, et al; Cooling and Surviving Septic Shock (CASS) Trial Collaboration: Induced hypothermia in patients with septic shock and respiratory failure (CASS): A randomised, controlled, open-label trial. *Lancet Respir Med* 2018; 6:183–192
61. Girard TD, Exline MC, Carson SS, et al; MIND-USA Investigators: Haloperidol and ziprasidone for treatment of delirium in critical illness. *N Engl J Med* 2018; 379:2506–2516
62. Chapman M, Peake SL, Bellomo R, et al; TARGET Investigators, for the ANZICS Clinical Trials Group: Energy-dense versus routine enteral nutrition in the critically ill. *N Engl J Med* 2018; 379:1823–1834
63. Simonis FD, Serpa Neto A, Binnekade JM, et al; Writing Group for the PReVENT Investigators: Effect of a low vs intermediate tidal volume strategy on ventilator-free days in intensive care unit patients without ARDS: A randomized clinical trial. *JAMA* 2018; 320:1872–1880
64. Pinder EM, Rostron AJ, Hellyer TP, et al: Randomised controlled trial of GM-CSF in critically ill patients with impaired neutrophil phagocytosis. *Thorax* 2018; 73:918–925
65. Dellinger RP, Bagshaw SM, Antonelli M, et al; EUPHRATES Trial Investigators: Effect of targeted polymyxin B hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level: The EUPHRATES randomized clinical trial. *JAMA* 2018; 320:1455–1463
66. Barbar SD, Clere-Jehl R, Bourredjem A, et al; IDEAL-ICU Trial Investigators and the CRICS TRIGGERSEP Network: Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. *N Engl J Med* 2018; 379:1431–1442
67. van Meenen DMP, van der Hoeven SM, Binnekade JM, et al: Effect of on-demand vs routine nebulization of acetylcysteine with salbutamol on ventilator-free days in intensive care unit patients receiving invasive ventilation: A randomized clinical trial. *JAMA* 2018; 319:993–1001
68. Reignier J, Boisramé-Helms J, Brisard L, et al; NUTRIREA-2 Trial Investigators; Clinical Research in Intensive Care and Sepsis (CRICS) group: Enteral versus parenteral early nutrition in ventilated adults with shock: A randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). *Lancet* 2018; 391:133–143
69. Combes A, Hajage D, Capellier G, et al; EOLIA Trial Group, REVA, and ECMONet: Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 378:1965–1975
70. van den Boogaard M, Slooter AJC, Brüggemann RJM, et al; REDUCE Study Investigators: Effect of haloperidol on survival among critically ill adults with a high risk of delirium: The REDUCE randomized clinical trial. *JAMA* 2018; 319:680–690
71. Venkatesh B, Finfer S, Cohen J, et al; ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group: Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018; 378:797–808
72. Khanna A, English SW, Wang XS, et al; ATHOS-3 Investigators: Angiotensin II for the treatment of vasodilatory shock. *N Engl J Med* 2017; 377:419–430
73. Cooper DJ, McQuilten ZK, Nichol A, et al; TRANSFUSE Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group: Age of red cells for transfusion and outcomes in critically ill adults. *N Engl J Med* 2017; 377:1858–1867
74. Futier E, Lefrant JY, Guinot PG, et al; INPRESS Study Group: Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: A randomized clinical trial. *JAMA* 2017; 318:1346–1357
75. Landoni G, Lomivorotov VV, Alvaro G, et al; CHEETAH Study Group: Levosimendan for hemodynamic support after cardiac surgery. *N Engl J Med* 2017; 376:2021–2031
76. Wischmeyer PE, Hasselmann M, Kummerlen C, et al: A randomized trial of supplemental parenteral nutrition in underweight and overweight critically ill patients: The TOP-UP pilot trial. *Crit Care* 2017; 21:142
77. Valette X, Desmeulles I, Savary B, et al: Sodium bicarbonate versus sodium chloride for preventing contrast-associated acute kidney injury in critically ill patients: A randomized controlled trial. *Crit Care Med* 2017; 45:637–644
78. van der Geest PJ, Mohseni M, Nieboer D, et al: Procalcitonin to guide taking blood cultures in the intensive care unit; a cluster-randomized controlled trial. *Clin Microbiol Infect* 2017; 23:86–91
79. Qiu C, Chen C, Zhang W, et al: Fat-modified enteral formula improves feeding tolerance in critically ill patients: A multicenter, single-blind, randomized controlled trial. *JPEN J Parenter Enteral Nutr* 2017; 41:785–795
80. Keh D, Trips E, Marx G, et al; SepNet–Critical Care Trials Group: Effect of hydrocortisone on development of shock among patients

with severe sepsis: The HYPRESS randomized clinical trial. *JAMA* 2016; 316:1775–1785

81. Park JT, Lee H, Kee YK, et al; HICORES Investigators: High-dose versus conventional-dose continuous venovenous hemodiafiltration and patient and kidney survival and cytokine removal in sepsis-associated acute kidney injury: A randomized controlled trial. *Am J Kidney Dis* 2016; 68:599–608
82. Bloos F, Trips E, Nierhaus A, et al; for SepNet Critical Care Trials Group: Effect of sodium selenite administration and procalcitonin-guided therapy on mortality in patients with severe sepsis or septic shock: A randomized clinical trial. *JAMA Intern Med* 2016; 176:1266–1276
83. Donnino MW, Andersen LW, Berg KM, et al; Collaborating Authors from the Beth Israel Deaconess Medical Center's Center for Resuscitation Science Research Group: Corticosteroid therapy in refractory shock following cardiac arrest: A randomized, double-blind, placebo-controlled, trial. *Crit Care* 2016; 20:82
84. Faisy C, Meziani F, Planquette B, et al; DIABOLO Investigators: Effect of acetazolamide vs placebo on duration of invasive mechanical ventilation among patients with chronic obstructive pulmonary disease: A randomized clinical trial. *JAMA* 2016; 315:480–488
85. Legriel S, Lemiale V, Schenck M, et al; HYBERNATUS Study Group: Hypothermia for neuroprotection in convulsive status epilepticus. *N Engl J Med* 2016; 375:2457–2467
86. Wiberg S, Hassager C, Schmidt H, et al: Neuroprotective effects of the glucagon-like peptide-1 analog exenatide after out-of-hospital cardiac arrest: A randomized controlled trial. *Circulation* 2016; 134:2115–2124
87. Kacmarek RM, Villar J, Sulemanji D, et al; Open Lung Approach Network: Open lung approach for the acute respiratory distress syndrome: A pilot, randomized controlled trial. *Crit Care Med* 2016; 44:32–42
88. Ziegler TR, May AK, Hebbar G, et al: Efficacy and safety of glutamine-supplemented parenteral nutrition in surgical ICU patients: An American multicenter randomized controlled trial. *Ann Surg* 2016; 263:646–655
89. Cavalcanti AB, Bozza FA, Machado FR et al: Effect of a quality improvement intervention with daily round checklists, goal setting, and clinician prompting on mortality of critically ill patients: A randomized clinical trial. *JAMA* 2016; 315:1480–1490
90. Gaudry S, Hajage D, Schortgen F, et al; AKIKI Study Group: Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 2016; 375:122–133
91. Torres A, Sibila O, Ferrer M, et al: Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: A randomized clinical trial. *JAMA* 2015; 313:677–686
92. Payen DM, Guilhot J, Launey Y, et al; ABDOMIX Group: Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: A multicenter randomized control trial. *Intensive Care Med* 2015; 41:975–984
93. Deye N, Cariou A, Girardie P, et al; Clinical and Economical Impact of Endovascular Cooling in the Management of Cardiac Arrest (ICEREA) Study Group: Endovascular versus external targeted temperature management for patients with out-of-hospital cardiac arrest: A randomized, controlled study. *Circulation* 2015; 132:182–193
94. Lacroix J, Hébert PC, Fergusson DA, et al; ABLE Investigators; Canadian Critical Care Trials Group: Age of transfused blood in critically ill adults. *N Engl J Med* 2015; 372:1410–1418
95. Combes A, Bréchot N, Amour J, et al: Early high-volume hemofiltration versus standard care for post-cardiac surgery shock. The HEROICS study. *Am J Respir Crit Care Med* 2015; 192:1179–1190
96. Lemiale V, Mokart D, Resche-Rigon M, et al; Groupe de Recherche en Réanimation Respiratoire du patient d'Onco-Hématologie (GRRR-OH): Effect of noninvasive ventilation vs oxygen therapy on mortality among immunocompromised patients with acute respiratory failure: A randomized clinical trial. *JAMA* 2015; 314:1711–1719
97. Vincent JL, Marshall JC, Dellinger RP, et al; Oral tAlactoferrin in Severe sepsIS Study Investigators: Talactoferrin in severe sepsis: Results from the phase II/III oral tAlactoferrin in severe sepsIS trial. *Crit Care Med* 2015; 43:1832–1838
98. Mouncey PR, Osborn TM, Power GS, et al; ProMISe Trial Investigators: Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015; 372:1301–1311
99. Peake SL, Delaney A, Bailey M, et al: Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014; 371:1496–1506
100. Yealy DM, Kellum JA, Huang DT et al: A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014; 370:1683–1693
101. van Zanten AR, Sztark F, Kaisers UX, et al: High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: A randomized clinical trial. *JAMA* 2014; 312:514–524
102. Abroug F, Ouanes-Besbes L, Fkih-Hassen M, et al: Prednisone in COPD exacerbation requiring ventilatory support: An open-label randomised evaluation. *Eur Respir J* 2014; 43:717–724
103. Giamarellos-Bourboulis EJ, Mylona V, Antonopoulou A, et al: Effect of clarithromycin in patients with suspected gram-negative sepsis: Results of a randomized controlled trial. *J Antimicrob Chemother* 2014; 69:1111–1118
104. Asfar P, Meziani F, Hamel JF, et al; SEPSISPAM Investigators: High versus low blood-pressure target in patients with septic shock. *N Engl J Med* 2014; 370:1583–1593
105. Caironi P, Tognoni G, Masson S, et al; ALBIOS Study Investigators: Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014; 370:1412–1421
106. Leaf DE, Waikar SS: Rosuvastatin for sepsis-associated ARDS. *N Engl J Med* 2014; 371:968
107. Holst LB, Haase N, Wetterslev J, et al; TRISS Trial Group; Scandinavian Critical Care Trials Group: Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med* 2014; 371:1381–1391
108. Harvey SE, Parrott F, Harrison DA, et al; CALORIES Trial Investigators: Trial of the route of early nutritional support in critically ill adults. *N Engl J Med* 2014; 371:1673–1684
109. Young D, Harrison DA, Cuthbertson BH, et al; TracMan Collaborators: Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: The TracMan randomized trial. *JAMA* 2013; 309:2121–2129
110. Opal SM, Laterre PF, Francois B, et al; ACCESS Study Group: Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: The ACCESS randomized trial. *JAMA* 2013; 309:1154–1162
111. Papazian L, Roch A, Charles PE, et al; STATIN-VAP Study Group: Effect of statin therapy on mortality in patients with ventilator-associated pneumonia: A randomized clinical trial. *JAMA* 2013; 310:1692–1700
112. Annane D, Timsit JF, Megarbane B, et al; APROCCHSS Trial Investigators: Recombinant human activated protein C for adults with septic shock: A randomized controlled trial. *Am J Respir Crit Care Med* 2013; 187:1091–1097
113. Young D, Lamb SE, Shah S, et al; OSCAR Study Group: High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med* 2013; 368:806–813
114. Hung IFN, To KKW, Lee CK, et al: Hyperimmune IV immunoglobulin treatment: A multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. *Chest* 2013; 144:464–473
115. Vincent JL, Ramesh MK, Ernest D, et al: A randomized, double-blind, placebo-controlled, phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation. *Crit Care Med* 2013; 41:2069–2079
116. Annane D, Siami S, Jaber S, et al; CRISTAL Investigators: Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: The CRISTAL randomized trial. *JAMA* 2013; 310:1809–1817
117. Doig GS, Simpson F, Sweetman EA, et al; Early PN Investigators of the ANZICS Clinical Trials Group: Early parenteral nutrition in critically ill patients with short-term relative contraindications to

early enteral nutrition: A randomized controlled trial. *JAMA* 2013; 309:2130–2138

118. Durante-Mangoni E, Signoriello G, Andini R, et al: Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant acinetobacter baumannii: A multicenter, randomized clinical trial. *Clin Infect Dis* 2013; 57:349–358
119. Vignon P, Dequin PF, Renault A, et al; Clinical Research in Intensive Care and Sepsis Group (CRICS Group): Intermittent pneumatic compression to prevent venous thromboembolism in patients with high risk of bleeding hospitalized in intensive care units: The CIREA1 randomized trial. *Intensive Care Med* 2013; 39:872–880
120. Myburgh JA, Finfer S, Bellomo R, et al; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367:1901–1911
121. Ranieri VM, Thompson BT, Barie PS, et al; PROWESS-SHOCK Study Group: Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 2012; 366:2055–2064
122. Thiele H, Zeymer U, Neumann FJ, et al; IABP-SHOCK II Trial Investigators: Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012; 367:1287–1296
123. Jensen JU, Hein L, Lundgren B, et al; Procalcitonin And Survival Study (PASS) Group: Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: A randomized trial. *Crit Care Med* 2011; 39:2048–2058
124. Wunderink RG, Laterre PF, Francois B, et al; CAPTIVATE Trial Group: Recombinant tissue factor pathway inhibitor in severe community-acquired pneumonia: A randomized trial. *Am J Respir Crit Care Med* 2011; 183:1561–1568
125. Spragg RG, Taut FJ, Lewis JF, et al: Recombinant surfactant protein C-based surfactant for patients with severe direct lung injury. *Am J Respir Crit Care Med* 2011; 183:1055–1061
126. Jansen TC, van Bommel J, Schoonderbeek FJ, et al; LACTATE study group: Early lactate-guided therapy in intensive care unit patients: A multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med* 2010; 182:752–761
127. Peek GJ, Mugford M, Tiruvoipati R, et al; CESAR trial collaboration: Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomised controlled trial. *Lancet* 2009; 374:1351–1363
128. Jones AE, Shapiro NI, Trzeciak S, et al; Emergency Medicine Shock Research Network (EMShockNet) Investigators: Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: A randomized clinical trial. *JAMA* 2010; 303:739–746
129. Rice TW, Wheeler AP, Bernard GR, et al: A randomized, double-blind, placebo-controlled trial of TAK-242 for the treatment of severe sepsis. *Crit Care Med* 2010; 38:1685–1694
130. Annane D, Cariou A, Maxime V et al: Corticosteroid treatment and intensive insulin therapy for septic shock in adults: A randomized controlled trial. *JAMA* 2010; 303:341–348
131. Bouadma L, Luyt CE, Tubach F, et al; PRORATA trial group: Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): A multicentre randomised controlled trial. *Lancet* 2010; 375:463–474
132. Tidswell M, Tillis W, Larosa SP, et al; Eritoran Sepsis Study Group: Phase 2 trial of eritoran tetrasodium (E5564), a toll-like receptor 4 antagonist, in patients with severe sepsis. *Crit Care Med* 2010; 38:72–83
133. Hauser CJ, Boffard K, Dutton R, et al; CONTROL Study Group: Results of the CONTROL trial: Efficacy and safety of recombinant activated factor VII in the management of refractory traumatic hemorrhage. *J Trauma* 2010; 69:489–500
134. Taccone P, Pesenti A, Latini R, et al; Prone-Supine II Study Group: Prone positioning in patients with moderate and severe acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2009; 302:1977–1984
135. Palizas F, Dubin A, Regueira T, et al: Gastric tonometry versus cardiac index as resuscitation goals in septic shock: A multicenter, randomized, controlled trial. *Crit Care* 2009; 13:R44
136. Bellomo R, Cass A, Cole L et al: Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009; 361:1627–1638
137. Dellinger RP, Tomayko JF, Angus DC, et al; Lipid Infusion and Patient Outcomes in Sepsis (LIPOS) Investigators: Efficacy and safety of a phospholipid emulsion (GR270773) in Gram-negative severe sepsis: Results of a phase II multicenter, randomized, placebo-controlled, dose-finding clinical trial. *Crit Care Med* 2009; 37:2929–2938
138. Kesecioglu J, Beale R, Stewart TE, et al: Exogenous natural surfactant for treatment of acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2009; 180:989–994
139. Lins RL, Elseviers MM, Van der Niepen P, et al; SHARF investigators: Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: Results of a randomized clinical trial. *Nephrol Dial Transplant* 2009; 24:512–518
140. Preiser JC, Devos P, Ruiz-Santana S, et al: A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: The Glucontrol study. *Intensive Care Med* 2009; 35:1738–1748
141. Schuetz P, Christ-Crain M, Thomann R, et al; ProHOSP Study Group: Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: The ProHOSP randomized controlled trial. *JAMA* 2009; 302:1059–1066
142. Doig GS, Simpson F, Finfer S, et al; Nutrition Guidelines Investigators of the ANZICS Clinical Trials Group: Effect of evidence-based feeding guidelines on mortality of critically ill adults: A cluster randomized controlled trial. *JAMA* 2008; 300:2731–2741
143. Blot F, Similowski T, Trouillet JL, et al: Early tracheotomy versus prolonged endotracheal intubation in unselected severely ill ICU patients. *Intensive Care Med* 2008; 34:1779–1787
144. Palevsky PM, Zhang JH, O'Connor TZ et al: Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008; 359:7–20
145. Russell JA, Walley KR, Singer J, et al; VASST Investigators: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–887
146. Mercat A, Richard JC, Vielle B, et al; Expiratory Pressure (Express) Study Group: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:646–655
147. Meade MO, Cook DJ, Guyatt GH, et al; Lung Open Ventilation Study Investigators: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:637–645
148. Brunkhorst FM, Engel C, Bloos F, et al; German Competence Network Sepsis (SepNet): Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; 358:125–139
149. Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111–124
150. Giamarellos-Bourboulis EJ, Pechère JC, Routsi C, et al: Effect of clarithromycin in patients with sepsis and ventilator-associated pneumonia. *Clin Infect Dis* 2008; 46:1157–1164
151. Tumlin J, Wali R, Williams W, et al: Efficacy and safety of renal tubule cell therapy for acute renal failure. *J Am Soc Nephrol* 2008; 19:1034–1040
152. Fernandez R, Trenchs X, Klamburg J, et al: Prone positioning in acute respiratory distress syndrome: A multicenter randomized clinical trial. *Intensive Care Med* 2008; 34:1487–1491
153. Heyland DK, Dodek P, Muscedere J, et al; Canadian Critical Care Trials Group: Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. *Crit Care Med* 2008; 36:737–744
154. Kinasewitz GT, Privalle CT, Imm A, et al: Multicenter, randomized, placebo-controlled study of the nitric oxide scavenger pyridoxalated hemoglobin polyoxyethylene in distributive shock. *Crit Care Med* 2008; 36:1999–2007
155. Werdan K, Pilz G, Müller-Werdan U, et al; Early Supplemental Severe SIRS Treatment With IVIG in Score-Identified High-Risk Patients

After Cardiac Surgery (ESSICS) Study Group: Immunoglobulin G treatment of postcardiac surgery patients with score-identified severe systemic inflammatory response syndrome–the ESSICS study. *Crit Care Med* 2008; 36:716–723

156. Manzano F, Fernández-Mondéjar E, Colmenero M, et al: Positive-end expiratory pressure reduces incidence of ventilator-associated pneumonia in nonhypoxemic patients. *Crit Care Med* 2008; 36:2225–2231
157. Werdan K, Pilz G, Bujdoso O, et al; Score-Based Immunoglobulin Therapy of Sepsis (SBITS) Study Group: Score-based immunoglobulin G therapy of patients with sepsis: The SBITS study. *Crit Care Med* 2007; 35:2693–2701
158. Moritz F, Brousse B, Gellée B, et al: Continuous positive airway pressure versus bilevel noninvasive ventilation in acute cardiogenic pulmonary edema: A randomized multicenter trial. *Ann Emerg Med* 2007; 50:666–675, 675.e1
159. Annane D, Vignon P, Renault A, et al; CATS Study Group: Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: A randomised trial. *Lancet* 2007; 370:676–684
160. Levi M, Levy M, Williams MD, et al; Xigris and Prophylactic HepaRin Evaluation in Severe Sepsis (XPRESS) Study Group: Prophylactic heparin in patients with severe sepsis treated with drotrecogin alfa (activated). *Am J Respir Crit Care Med* 2007; 176:483–490
161. Stoutenbeek CP, van Saene HK, Miranda DR, et al: The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. *Intensive Care Med* 1984; 10:185–192
162. Angstwurm MW, Engelmann L, Zimmermann T, et al: Selenium in Intensive Care (SIC): Results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. *Crit Care Med* 2007; 35:118–126
163. van Ruler O, Mahler CW, Boer KR, et al; Dutch Peritonitis Study Group: Comparison of on-demand vs planned relaparotomy strategy in patients with severe peritonitis: A randomized trial. *JAMA* 2007; 298:865–872
164. Hentrich M, Fehnle K, Ostermann H, et al: IgMA-enriched immunoglobulin in neutropenic patients with sepsis syndrome and septic shock: A randomized, controlled, multiple-center trial. *Crit Care Med* 2006; 34:1319–1325
165. Canadian Critical Care Trials Group: A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *N Engl J Med* 2006; 355:2619–2630
166. Radrizzani D, Bertolini G, Facchini R, et al: Early enteral immunonutrition vs. parenteral nutrition in critically ill patients without severe sepsis: A randomized clinical trial. *Intensive Care Med* 2006; 32:1191–1198
167. Wheeler AP, Bernard GR, Thompson BT et al: Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 2006; 354:2213–2224
168. Wiedemann HP, Wheeler AP, Bernard GR et al: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354:2564–2575
169. Steinberg KP, Hudson LD, Goodman RB, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1671–1684
170. Mancebo J, Fernández R, Blanch L, et al: A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; 173:1233–1239
171. Vinsonneau C, Camus C, Combes A, et al; Hemodiafe Study Group: Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: A multicentre randomised trial. *Lancet* 2006; 368:379–385
172. Rodríguez A, Rello J, Neira J, et al: Effects of high-dose of intravenous immunoglobulin and antibiotics on survival for severe sepsis undergoing surgery. *Shock* 2005; 23:298–304
173. Harvey S, Harrison DA, Singer M, et al; PAC-Man study collaboration: Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): A randomised controlled trial. *Lancet* 2005; 366:472–477
174. Abraham E, Laterre PF, Garg R, et al; Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group: Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005; 353:1332–1341
175. Tumlin JA, Finkel KW, Murray PT, et al: Fenoldopam mesylate in early acute tubular necrosis: A randomized, double-blind, placebo-controlled clinical trial. *Am J Kidney Dis* 2005; 46:26–34
176. Zeiher BG, Steingrub J, Laterre PF, et al; EZZI Study Group: LY315920NA/S-5920, a selective inhibitor of group IIA secretory phospholipase A2, fails to improve clinical outcome for patients with severe sepsis. *Crit Care Med* 2005; 33:1741–1748
177. Guerin C, Gaillard S, Lemasson S, et al: Effects of systematic prone positioning in hypoxemic acute respiratory failure: A randomized controlled trial. *JAMA* 2004; 292:2379–2387
178. Spragg RG, Lewis JF, Walmrath HD, et al: Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. *N Engl J Med* 2004; 351:884–892
179. Brower RG, Lanken PN, MacIntyre N, et al; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351:327–336
180. Albrecht DM, van Ackern K, Bender HJ, et al: Efficacy and safety of the platelet-activating factor receptor antagonist BN 52021 (Ginkgolide B) in patients with severe sepsis: A randomised, double-blind, placebo-controlled, multicentre trial. *Clin Drug Investig* 2004; 24:137–147
181. Finfer S, Bellomo R, Boyce N, et al; SAFE Study Investigators: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350:2247–2256
182. Opal S, Laterre PF, Abraham E, et al; Controlled Mortality Trial of Platelet-Activating Factor Acetylhydrolase in Severe Sepsis Investigators: Recombinant human platelet-activating factor acetylhydrolase for treatment of severe sepsis: Results of a phase III, multicenter, randomized, double-blind, placebo-controlled, clinical trial. *Crit Care Med* 2004; 32:332–341
183. Abraham E, Naum C, Bandi V, et al: Efficacy and safety of LY315920Na/S-5920, a selective inhibitor of 14-kDa group IIA secretory phospholipase A2, in patients with suspected sepsis and organ failure. *Crit Care Med* 2003; 31:718–728
184. Abraham E, Reinhart K, Opal S, et al; OPTIMIST Trial Study Group: Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: A randomized controlled trial. *JAMA* 2003; 290:238–247
185. Albertson TE, Panacek EA, MacArthur RD, et al; MAB-T88 Sepsis Study Group: Multicenter evaluation of a human monoclonal antibody to Enterobacteriaceae common antigen in patients with Gram-negative sepsis. *Crit Care Med* 2003; 31:419–427
186. Chastre J, Wolff M, Fagon JY, et al; PneumA Trial Group: Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: A randomized trial. *JAMA* 2003; 290:2588–2598
187. Richard C, Warszawski J, Anguel N, et al; French Pulmonary Artery Catheter Study Group: Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2003; 290:2713–2720
188. Root RK, Lodato RF, Patrick W, et al; Pneumonia Sepsis Study Group: Multicenter, double-blind, placebo-controlled study of the use of filgrastim in patients hospitalized with pneumonia and severe sepsis. *Crit Care Med* 2003; 31:367–373
189. Sandham JD, Hull RD, Brant RF, et al; Canadian Critical Care Clinical Trials Group: A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003; 348:5–14
190. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, et al: Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: A prospective, randomized trial. *Crit Care Med* 2002; 30:2205–2211
191. Reinhart K, Menges T, Gardlund B, et al: Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment

afelimomab in hyperinflammatory response during severe sepsis: The RAMSES Study. *Crit Care Med* 2001; 29:765–769

192. Abraham E, Laterre PF, Garbino J, et al; Lenercept Study Group: Lenercept (p55 tumor necrosis factor receptor fusion protein) in severe sepsis and early septic shock: A randomized, double-blind, placebo-controlled, multicenter phase III trial with 1,342 patients. *Crit Care Med* 2001; 29:503–510
193. Gattinoni L, Tognoni G, Pesenti A, et al; Prone-Supine Study Group: Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001; 345:568–573
194. Vincent JL, Brase R, Santman F, et al: A multi-centre, double-blind, placebo-controlled study of liposomal prostaglandin E1 (TLC C-53) in patients with acute respiratory distress syndrome. *Intensive Care Med* 2001; 27:1578–1583
195. Warren BL, Eid A, Singer P, et al; KyberSept Trial Study Group: Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: A randomized controlled trial. *JAMA* 2001; 286:1869–1878
196. Angus DC, Birmingham MC, Balk RA, et al: E5 murine monoclonal antiendotoxin antibody in gram-negative sepsis: A randomized controlled trial. E5 Study Investigators. *JAMA* 2000; 283:1723–1730
197. The ARDS Network: Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2000; 283:1995–2002
198. Poeze M, Froon AH, Ramsay G, et al: Decreased organ failure in patients with severe SIRS and septic shock treated with the platelet-activating factor antagonist TCV-309: A prospective, multicenter, double-blind, randomized phase II trial. TCV-309 Septic Shock Study Group. *Shock* 2000; 14:421–428
199. Takala J, Meier-Hellmann A, Eddleston J, et al: Effect of dopexamine on outcome after major abdominal surgery: A prospective, randomized, controlled multicenter study. European Multicenter Study Group on Dopexamine in Major Abdominal Surgery. *Crit Care Med* 2000; 28:3417–3423
200. Demetriades D, Smith JS, Jacobson LE, et al: Bactericidal/permeability-increasing protein (rBPI21) in patients with hemorrhage due to trauma: Results of a multicenter phase II clinical trial. rBPI21 Acute Hemorrhagic Trauma Study Group. *J Trauma* 1999; 46:667–676; discussion 676–677
201. Hébert PC, Wells G, Blajchman MA, et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; 340:409–417
202. Abraham E, Anzueto A, Gutierrez G, et al: Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. NORASEPT II Study Group. *Lancet* 1998; 351:929–933
203. Brochard L, Roudot-Thoraval F, Roupie E, et al: Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on tidal volume reduction in ARDS. *Am J Respir Crit Care Med* 1998; 158:1831–1838
204. Dhainaut JF, Tenaillon A, Hemmer M, et al: Confirmatory platelet-activating factor receptor antagonist trial in patients with severe gram-negative bacterial sepsis: A phase III, randomized, double-blind, placebo-controlled, multicenter trial. BN 52021 Sepsis Investigator Group. *Crit Care Med* 1998; 26:1963–1971
205. Wasserman D, Ioannovich JD, Hinzmann RD, et al: Interferon-gamma in the prevention of severe burn-related infections: A European phase III multicenter trial. The Severe Burns Study Group. *Crit Care Med* 1998; 26:434–439
206. Opal SM, Fisher CJ Jr, Dhainaut JF, et al: Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: A phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med* 1997; 25:1115–1124
207. Anzueto A, Baughman RP, Guntupalli KK, et al: Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. Exosurf Acute Respiratory Distress Syndrome Sepsis Study Group. *N Engl J Med* 1996; 334:1417–1421
208. Cohen J, Carlet J: INTERSEPT: An international, multicenter, placebo-controlled trial of monoclonal antibody to human tumor necrosis factor-alpha in patients with sepsis. International Sepsis Trial Study Group. *Crit Care Med* 1996; 24:1431–1440
209. Abraham E, Wunderink R, Silverman H, et al: Efficacy and safety of monoclonal antibody to human tumor necrosis factor alpha in patients with sepsis syndrome. A randomized, controlled, double-blind, multicenter clinical trial. TNF-alpha MAb Sepsis Study Group. *JAMA* 1995; 273:934–941
210. Bone RC, Balk RA, Fein AM, et al: A second large controlled clinical study of E5, a monoclonal antibody to endotoxin: Results of a prospective, multicenter, randomized, controlled trial. The E5 Sepsis Study Group. *Crit Care Med* 1995; 23:994–1006
211. Gattinoni L, Brazzi L, Pelosi P, et al: A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. *N Engl J Med* 1995; 333:1025–1032
212. Fisher CJ Jr, Dhainaut JF, Opal SM, et al: Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. *JAMA* 1994; 271:1836–1843
213. McCloskey RV, Straube RC, Sanders C, et al: Treatment of septic shock with human monoclonal antibody HA-1A. A randomized, double-blind, placebo-controlled trial. CHESS Trial Study Group. *Ann Intern Med* 1994; 121:1–5
214. Suter PM, Domenighetti G, Schaller MD, et al: N-acetylcysteine enhances recovery from acute lung injury in man. A randomized, double-blind, placebo-controlled clinical study. *Chest* 1994; 105:190–194
215. Gastinne H, Wolff M, Delatour F, et al: A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics. The French Study Group on Selective Decontamination of the Digestive Tract. *N Engl J Med* 1992; 326:594–599
216. Bone RC, Slotman G, Maunder R, et al: Randomized double-blind, multicenter study of prostaglandin E1 in patients with the adult respiratory distress syndrome. Prostaglandin E1 Study Group. *Chest* 1989; 96:114–119
217. Calandra T, Glauser MP, Schellekens J, et al: Treatment of gram-negative septic shock with human IgG antibody to escherichia coli J5: A prospective, double-blind, randomized trial. *J Infect Dis* 1988; 158:312–319
218. Bone RC, Fisher CJ Jr, Clemmer TP, et al: A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987; 317:653–658
219. Veterans Administration Systemic Sepsis Cooperative Study Group: Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. *N Engl J Med* 1987; 317:659–665
220. Jones CW, Handler L, Crowell KE, et al: Non-publication of large randomized clinical trials: Cross sectional analysis. *BMJ* 2013; 347:f6104
221. Moss M, Huang DT, Brower RG, et al; The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network: Early neuromuscular blockade in the acute respiratory distress syndrome. *N Engl J Med* 2019; 380:1997–2008
222. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
223. Brown CH, Ten Have TR, Jo B, et al: Adaptive designs for randomized trials in public health. *Annu Rev Public Health* 2009; 30:1–25
224. Opal SM, Dellinger RP, Vincent JL, et al: The next generation of sepsis clinical trial designs: What is next after the demise of recombinant human activated protein C?*. *Crit Care Med* 2014; 42:1714–1721
225. Park JJ, Thorlund K, Mills EJ: Critical concepts in adaptive clinical trials. *Clin Epidemiol* 2018; 10:343–351
226. de Grooth HJ, Geenen IL, Girbes AR, et al: SOFA and mortality endpoints in randomized controlled trials: A systematic review and meta-regression analysis. *Crit Care* 2017; 21:38
227. Herridge MS, Tansey CM, Matté A, et al; Canadian Critical Care Trials Group: Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; 364:1293–1304