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Update in Critical Care Medicine: Evidence Published in 2016

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We summarize key articles in critical care medicine published in 2016. We used an informal survey of academic and community intensivists to identify novel articles from high-impact journals that had important effects on clinical practice. In addition, we searched the most accessed journals from the American College of Physicians' JournalWise database to find articles that were particularly relevant to internal medicine clinicians.

We included 2 studies on acute respiratory distress syndrome (ARDS) that solidified the need to better understand the epidemiology of this disorder by demonstrating high rates of underrecognition and disparities in care. A novel noninvasive ventilation (NIV) device that may benefit patients with early ARDS was also identified, and lower oxygen targets may be appropriate. Studies of patients with severe sepsis showed no benefit of adjunctive steroid therapy; however, continuous infusion of antibiotics may significantly reduce mortality. Intensive blood pressure control does not seem to improve neurologic outcome in patients with acute intracerebral hemorrhage (ICH), and length of hospital stay may predict poor neurologic outcome and mortality in patients with in-hospital cardiac arrest. Progress was made in our understanding of the management of critically ill patients with acute kidney injury (AKI), as a randomized trial suggested that earlier initiation of renal replacement therapy (RRT) decreases mortality. Finally, depressive symptoms were shown to be highly prevalent in caregivers of critically ill patients, and strategies that provide social support to these persons should be identified.

ARDS and Acute Respiratory Failure

ARDS Often Goes Unrecognized or Underappreciated, Even in ICUs

Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315:788-800. [PMID: 26903337] doi:10.1001/jama.2016.0291

Background: Acute respiratory distress syndrome is defined by acute onset of bilateral alveolar or interstitial infiltrates, with impaired gas exchange in the absence of congestive heart failure (1). In patients with known ARDS, lung protective ventilation has proven benefit (2, 3), but evidence suggests that many patients for which this therapy would be appropriate are not receiving it (4, 5). Whether a diagnosis of ARDS affects what therapies the patient receives is also unclear, emphasizing the need for further epidemiologic data on this condition.

Findings: This multinational cohort included more than 29 000 patients admitted to participating intensive care units (ICUs). Of these patients, 10.4% fulfilled the criteria for ARDS, and most episodes occurred within 48 hours. Clinical recognition of ARDS varied from 51.3% in mild ARDS to 78.5% in severe ARDS. However, fewer than two thirds of patients with ARDS received a tidal volume of 8 mL per kg of ideal body weight or less, and plateau pressure was recorded in only 40.1%. Hospital mortality was 34.9% among patients with mild ARDS, 40.3% among those with moderate ARDS, and 46.1% among those with severe ARDS. The use of some adjunctive therapies that are recommended by some experts, such as neuromuscular blockade and prone positioning, increased with clinical recognition.

Cautions: The observational nature of this study precludes conclusions regarding the appropriateness of the interventions that patients received. In addition, an emerging literature suggests that individualized therapy for mechanical ventilation in ARDS may be reasonable (3, 6). Thus, analyses of large cohorts using a one-size-fits-all approach may result in inappropriate assumptions, because the therapeutic decisions that treating clinicians make on the basis of bedside observations and individual patient characteristics may be justifiable and reasonable.

Implications: Acute respiratory distress syndrome remains common and underrecognized, with substantial associated mortality. Treating clinicians should be aware of the epidemiology of ARDS so that proven therapies (lung protective ventilation) may be instituted promptly with early disease recognition and other therapies considered. Future ARDS trials will also depend on accurate and timely diagnosis.

ARDS-Related Mortality Is Decreasing, on the Basis of National Death Certificate Data

Cochi SE, Kempker JA, Annangi S, et al. Mortality trends of acute respiratory distress syndrome in the United States from 1999 to 2013. Ann Am Thorac Soc. 2016;13:1742-51. [PMID: 27403914]

Background: Substantial advances have been made in the treatment and understanding of ARDS over the past 2 decades (7–9). However, recent assessments of morbidity and mortality trends have been mostly limited to single-center studies in specific geographic regions (10, 11). Temporal and demographic trends in ARDS are also underinvestigated.

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Findings: Annual ARDS mortality in the United States from 1999 to 2013 was investigated by using the National Center for Health Statistics' Multiple Cause of Death (MCOD) database. This database comprises the recorded death certificate of every U.S. resident who died in the United States. The data include the underlying cause of death and up to 20 additional contributing diagnoses (based on International Classification of Diseases, 10th edition, codes), in addition to age category, race, ethnicity, sex, and geographic division at the time of death.

The MCOD data revealed that the overall number of deaths related to ARDS in the United States decreased from 13 612 in 1999 to 9762 in 2013, and the age-adjusted mortality rate decreased from 5.01 per 100 000 persons (95% CI, 4.92 to 5.09 per 100 000 persons) to 2.82 per 100 000 persons (CI, 2.76 to 2.88 per 100 000 persons). Males had a higher ARDS mortality rate (incident rate ratio,1.33 [CI, 1.26 to 1.41]) than females. The mortality rate was highest among African American persons compared with persons of other races or ethnicities, at 4.07 per 100 000 persons (CI, 4.01 to 4.12 per 100 000 persons). Mortality was highest in the winter and lowest in the summer.

Cautions: Diagnoses of ARDS were dependent on International Classification of Diseases coding practices, which vary among providers and institutions. Mortality trends in this study differed from those in previously published studies that used clinical definitions of ARDS, and were significantly lower overall. Variations in coding and documentation practices may account for these differences.

Implications: Mortality rates related to ARDS appear to be decreasing, yet these data obtained from death certificates may underestimate overall mortality. The mortality is highest in winter and lowest in summer. Racial disparities exist, with African American persons having the highest mortality rate. Because early identification is critical to optimal management, clinicians should be aware of these trends and characteristics of the disease.

Helmet NIV May Be Better Than Facemask NIV in Patients With ARDS

Patel BK, Wolfe KS, Pohlman AS, et al. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA. 2016;315:2435-41. [PMID: 27179847] doi:10.1001/jama.2016.6338

Background: Noninvasive ventilation has become the standard of care for management of patients with respiratory failure, particularly in the context of exacerbations of chronic obstructive pulmonary disease and congestive heart failure (12, 13). In addition, immunocompromised hosts (14), high-risk patients after extubation (15), and some patients during end-of-life care (16) may benefit from NIV. However, the optimal treatment of patients with hypoxemic respiratory failure of other causes (17) and the optimal method to accomplish either invasive or noninvasive ventilation of these patients remain unclear.

Findings: The investigators conducted a single-center, randomized clinical trial of 83 patients in the medical ICU who had ARDS requiring NIV delivered via facemask. Patients were randomly assigned to continue receiving NIV via facemask or to switch to NIV via a helmet (a transparent hood that covers the entire head).

The trial was stopped early after another randomized trial showed that facemask NIV is associated with a higher mortality rate than high-flow oxygen in acute hypoxemic respiratory failure (18). At the time the study was terminated, the intubation rate was 61.5% in the facemask group and 18.2% in the helmet group ($P < 0.001$). The helmet group also appeared to benefit from more ventilator-free days (28 vs. 12.5 days; $P < 0.001$) as well as improved mortality at 90 days (34.1% vs. 56.4%; $P = 0.02$). The findings support the role of helmet NIV in the management of ARDS.

Cautions: Although the observations are encouraging, the data are preliminary and will require corroboration in larger, multicenter clinical trials. The role of invasive versus noninvasive ventilation in ARDS also needs further study, as does the potential mechanisms underlying the benefits of helmet NIV (19). Ultimately, larger studies will be required to determine optimal ventilator management if NIV is being used and whether the cause of ARDS and other patient characteristics influence clinical management.

Implications: The use of NIV in ARDS will remain controversial until more definitive data emerge. However, sufficient data suggest potential benefits of high-flow oxygen or helmet NIV, leading some to question the value of facemask NIV. Clinicians should use facemask NIV with heightened caution in ARDS pending further study.

Too Much Oxygen May Be Deleterious in Patients With Respiratory Failure

Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: The Oxygen-ICU Randomized Clinical Trial. JAMA. 2016;316:1583-9. [PMID: 27706466] doi:10.1001/jama.2016.11993

Background: Supplemental oxygen is lifesaving for hypoxemic patients with chronic obstructive pulmonary disease and for patients with profound hypoxemia in the ICU. However, patients rarely die of hypoxemia itself, leading some to question the appropriate target goal when providing supplemental oxygen (20). Inadequate oxygen levels may lead to ischemia and anaerobic metabolism, whereas excessive oxygen may in theory be toxic and thus could be deleterious (21, 22).

Findings: The investigators conducted a single-center randomized trial in an Italian ICU. They randomly assigned 480 patients (of an originally planned sample of 660) before stopping the trial owing to difficulties in enrollment. Patients were randomly assigned to conventional oxygen saturation targets (97% to 100%) or

more conservative targets (94% to 98%). The resulting average oxygen tensions were higher in the conventional saturation group than the conservative group (102 mm Hg vs. 87 mm Hg). Mortality was lower in the conservative saturation group (11.6% vs. 20.2%; P = 0.01), with fewer episodes of shock, liver failure, or bacteremia.

Cautions: Although the results are intriguing, this was a single-center study that was stopped early; thus, the findings are preliminary and require corroboration. Prior human studies have shown somewhat equivocal results, leading to skepticism regarding the plausibility that the observed differences in oxygen tension were sufficient to yield the observed clinical impact.

Implications: Data are evolving that excessive oxygen supplementation may be problematic in animal models and in human studies. Judicious use of oxygen is recommended to avoid hypoxemia as well as hyperoxia. Further data are needed regarding the optimal strategy to provide oxygen.

Sepsis

Adjunctive Hydrocortisone Therapy Did Not Prevent Shock in Patients With Severe Sepsis

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;316:1775-85. [PMID: 27695824] doi:10.1001/jama.2016.14799

Background: Treatment with hydrocortisone is currently recommended for patients with sepsis and refractory or vasopressor-dependent shock (23). Although improved hemodynamics and more rapid reversal of shock has been consistently demonstrated, data on a potential mortality benefit with this approach remain controversial (24). Recently, adjunctive corticosteroid therapy has also been shown to offer clinical benefit in patients with sepsis due to community-acquired pneumonia despite an absence of shock (25), but this finding has not been demonstrated in other causes of sepsis or severe sepsis.

Findings: This double-blind, randomized, controlled trial conducted in 34 ICUs aimed to determine whether hydrocortisone therapy prevents the development of shock in septic patients without shock. The investigators randomly assigned 380 patients with sepsis, evidence of organ dysfunction, and absence of shock to receive either placebo or hydrocortisone, 200 mg/d, for 5 days, followed by a taper for 6 more days. The primary end point was occurrence of shock within 14 days.

The 2 groups did not differ statistically in the primary end point; 36 of 170 patients [21.2%] in the hydrocortisone group and 39 of 170 patients [22.9%] in the placebo group developed shock (difference, –1.8% [CI, –10.7% to 7%]; P = 0.70). Mortality at 28 days also did not differ between groups (8.8% vs. 8.2%; difference, 0.5% [CI, –5.6% to 6.7%]; P > 0.20). More hyperglycemic episodes occurred in the hydrocortisone group (90.9% vs. 81.5%; difference, 9.4% [CI, 2.4% to 16.4%]; P = 0.009).

Cautions: Data on baseline adrenal function were available only in a subgroup of patients from certain sites; thus, it is unclear whether patients with "relative adrenal insufficiency" (inadequate cortisol response) would have benefited from hydrocortisone therapy. Furthermore, the overall observed rate of septic shock in the placebo group was significantly lower than expected, making it more difficult to detect a clinically relevant change.

Implications: Severe sepsis progressing to septic shock carries a significant increase in mortality. This study shows that hydrocortisone therapy did not prevent progression to shock in these patients and was associated with a greater risk for hyperglycemia. This study argues against adjunctive hydrocortisone therapy in patients with sepsis without shock.

β-Lactam Antibiotics May Reduce Hospital Mortality in Severe Sepsis if Given as a Continuous Infusion Rather Than Intermittently

Roberts JA, Abdul-Aziz MH, Davis JS, et al. Continuous versus intermittent ß-lactam infusion in severe sepsis. A meta-analysis of individual patient data from randomized trials. Am J Respir Crit Care Med. 2016;194:681-91. [PMID: 26974879] doi:10.1164/rccm.201601-0024OC

Background: Although many randomized trials have failed to show benefits of various interventions for the treatment of sepsis, there is general agreement that early antimicrobial therapy and resuscitation are important components (26, 27). The timing of appropriate antibiotic therapy has been studied, but much less emphasis has been placed on how antimicrobials should be provided (28). Because the bactericidal effects of β-lactams are time-dependent, the duration that concentrations of these agents stay above the minimum inhibitory concentration for bacteria may be important; therefore, continuous dosing may have benefits over intermittent dosing, which entails inherent variability in plasma levels.

Findings: The investigators assessed 3 randomized, controlled trials of intermittent versus continuous β-lactam dosing in a total of 632 patients. Rates of hospital mortality and clinical cure for the continuous and the intermittent infusion groups were 19.6% versus 26.3% (relative risk, 0.74 [CI, 0.56 to 1.00]; P = 0.045) and 55.4% versus 46.3% (relative risk, 1.2 [CI, 1.03 to 1.40]; P = 0.021), respectively. In multivariate analyses, continuous β-lactam administration was independently and significantly associated with decreased hospital mortality. The findings provide rationale for further research in this area and for continuous infusion of β-lactam antibiotics in critically ill patients with severe sepsis.

Cautions: The findings included individual patient data aggregated from 3 individual trials (29–31) and thus should be regarded as hypothesis-generating rather than definitive. Larger data sets from randomized trials would allow corroboration of findings and assessment of potential issues, such as the effects of various pathogens and resistance patterns, the interaction with potentially synergistic antibiotics, and the source or site of infection.

Implications: Continuous infusion of β-lactams may be a reasonable approach to therapy in patients with severe sepsis in the ICU. Assuming that adequate intravenous access is available, the route of administration has a minimal effect on patient care. Antibiotic infusions could be implemented in the context of antibiotic stewardship programs to reduce unnecessary antibiotic exposure (for example, requiring daily reordering of antibiotic drip). Additional randomized trials on the effect of various antibiotic delivery approaches would be recommended.

Caring for Critically Ill Patients

Intensive Blood Pressure Lowering Does Not Improve Outcomes in Patients With Acute Hypertensive Response to Intracerebral Hemorrhage

Qureshi AI, Palesch YY, Barsan WG, et al; ATACH-2 Trial Investigators and the Neurological Emergency Treatment Trials Network. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Engl J Med. 2016;375:1033-43. [PMID: 27276234] doi:10.1056/NEJMoa1603460

Background: Acute hypertension is common in patients with ICH, and may lead to hematoma expansion and poor outcomes (32). Yet, data on the optimal blood pressure target in these patients are limited. A previous trial failed to demonstrate a benefit of intensive blood pressure control in hypertensive patients with ICH; however, many patients were enrolled beyond the time point of maximal hematoma expansion (3 to 4 hours) (33).

Findings: This study was designed to determine whether rapidly lowering the systolic blood pressure to an intensive target of 110 to 139 mm Hg in patients with an acute hypertensive response to ICH improved outcomes compared with a standard target of 140 to 179 mm Hg. Patients with supratentorial ICH less than 60 cm^3, a Glasgow Coma Scale score of 5 or more, and at least 1 systolic blood pressure reading of 180 mm Hg or greater were randomly assigned to the intensive or standard blood pressure target. Treatment was initiated within 4.5 hours after symptoms and continued for 24 hours. Intravenous nicardipine was the initial blood pressure lowering agent used in all patients.

Enrollment was stopped at 1000 participants because of futility. The primary outcome of death or moderately severe to severe disability (modified Rankin scale score of 4 to 6) at 3 months was observed in 186 of 481 patients (38.7%) in the intensive treatment group and 181 of 480 patients (37.7%) in the standard treatment group (relative risk, 1.04 [CI, 0.85 to 1.27]). The percentage of patients with hematoma expansion also did not differ between groups.

Cautions: Intravenous antihypertensive agents were used in the prerandomization period, and a higher percentage of patients in the intensive treatment group than the standard treatment group had primary treatment failure (12.2% vs. 0.8%). This imbalance may have blunted the ability to identify a potential treatment effect.

Implications: This study showed no improvement in the rate of death or disability when patients with an acute hypertensive response to ICH were treated to a systolic blood pressure target of 110 to 139 mm Hg compared with 140 to 179 mm Hg within 4.5 hours of symptoms. Acute hypertension after ICH carries a risk for poor outcome; however, the optimal systolic blood pressure target remains unclear.

Cardiac Arrest Mortality Increases With Duration of Hospital Stay, and Ventilatory-Related Arrests Become More Likely

Tran S, Deacon N, Minokadeh A, et al. Frequency and survival pattern of in-hospital cardiac arrests: the impacts of etiology and timing. Resuscitation. 2016;107:13-8. [PMID: 27456394] doi:10.1016/j.resuscitation.2016.07.006

Background: In-hospital cardiac arrests are associated with considerable morbidity and mortality (34). Outcome related to the cause of in-hospital cardiac arrest and length of hospital stay has not been well established.

Findings: The investigators hypothesized that survival and favorable neurologic outcome after in-hospital cardiac arrest were inversely proportional to hospital day. To investigate this hypothesis, they performed a retrospective cohort study of patients admitted to a single hospital system who had a first arrest during a single hospitalization. The primary outcome was survival to discharge, which was evaluated on the basis of duration of hospitalization. There were 627 cardiac arrests identified that fit the inclusion criteria, and these events were divided into 3 groups on the basis of the hospital day on which the cardiac arrest occurred (hospital day 1, 2 to 7, or >7). Multivariable logistic regression analysis was performed to evaluate hospital day as an independent predictor of survival and favorable neurologic outcome.

Both survival and favorable neurologic outcome significantly decreased with increasing hospital days ($P = 0.038$ and 0.002, respectively). Survival was 38.9% (CI, 32.0% to 45.7%) for hospital day 1, 34.0% (CI, 27.5% to 40.4%) for hospital day 2 to 7, and 27.2% (CI, 21.4% to 33.0%) for hospital day 7 or more. With increasing length of hospital stay, the proportion of arrests related to dysrhythmias decreased ($P = 0.014$), whereas those related to ventilatory failure increased ($P = 0.001$).

Cautions: This study was done at a single academic institution that uses a comprehensive resuscitation program to train all in-hospital providers. Its retrospective, observational design may limit the generalizability of the findings to other settings and precludes establishing conclusions regarding a cause–effect relationship between hospital day and cause of arrest.
Implications: Cause of in-hospital cardiac arrests varies by length of hospital stay, with arrests due to impaired ventilation becoming more frequent; in addition, survival to discharge decreases with increasing length of stay. These findings may be useful in guiding clinicians in cardiac arrest prevention and management, as well as in code status counseling and end-of-life care. However, further studies evaluating the impact of increasing hospital length of stay on cause of cardiac arrest and its prevention will be required.

Critically Ill Patients With AKI May Benefit From Earlier Initiation of RRT

Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN Randomized Clinical Trial. JAMA. 2016;315:2190-9. [PMID: 27209269] doi:10.1001/jama.2016.5828

Background: Initiating dialysis earlier in the course of AKI may prevent complications, and optimal timing of RRT has been recently investigated (35). Prior data have been conflicting but have demonstrated that large trials investigating early versus late initiation of RRT are safe and feasible (36).
Findings: This randomized, single-center, parallel-group trial compared early and delayed initiation of RRT in critically ill patients with AKI. Patients with Kidney Disease: Improving Global Outcomes (KDIGO) stage 2 AKI (2-fold increase in serum creatinine concentration from baseline or urine output <0.5 mL/kg per hour for 12 hours) and plasma neutrophil gelatinase-associated lipocalin level greater than 150 ng/mL were randomly assigned to early initiation of RRT (within 8 hours of diagnosis of KDIGO stage 2 AKI) or delayed initiation (within 12 hours of stage 3 AKI [3-fold increase in serum creatinine concentration or urine output <0.3 mL/kg per hour for 24 hours]). Additional absolute indications for RRT included severe acid–base or electrolyte abnormalities, severe uremia, and diuretic-resistant edema. The primary outcome evaluated was mortality at 90 days after randomization.

A total of 231 patients were enrolled. All 112 patients in the early initiation group received RRT, compared with 108 of 119 patients in the delayed initiation group. There was significantly reduced 90-day mortality in the early RRT group compared with the delayed RRT group (44 of 112 patients [39.3%] vs. 65 of 119 patients [54.7%]; hazard ratio [HR], 0.66 [CI, 0.45 to 0.97]; $P = 0.03$). Secondary outcomes, including duration of RRT, duration of mechanical ventilation, and hospital length of stay, were also significantly reduced in the early RRT group. Levels of the inflammatory mediators interleukin (IL)-6 and IL-8 were significantly reduced in the early RRT group.
Cautions: This was a single-center trial; thus, its reproducibility and generalizability are unclear. Almost all participants were surgical patients, and the conclusions are therefore limited to the population studied.
Implications: Early initiation of RRT in critically ill patients with AKI may reduce 90-day mortality compared with delayed initiation. A reduction in systemic inflammation, as evidenced by reduced IL-6 and IL-8 levels, is a potential mechanism. Further investigation in a large, multicenter trial is warranted.

Caregivers of ICU Patients Have Depressive Symptoms That May Persist for at Least 1 Year

Cameron JI, Chu LM, Matte A, et al; RECOVER Program Investigators (Phase 1: towards RECOVER). One-year outcomes in caregivers of critically ill patients. N Engl J Med. 2016;374:1831-41. [PMID: 27168433] doi:10.1056/NEJMoa1511160

Background: The traditional focus in the ICU has been on 28-day survival, with minimal attention paid to what goes on after the first month of critical illness. More recently, attention has been drawn to the important issue of longer-term outcomes of patients and providers, including the potential for burnout of ICU care providers (37). However, the impact of critical illness and the recovery process on the patients' families has not been a major topic of discussion.
Findings: The investigators enrolled 280 caregivers of patients who received at least 7 days of mechanical ventilation in the ICU. The caregivers underwent structured interviews to assess mental health and quality of life. A large percentage of the caregivers reported symptoms of depression (67% initially and 43% at 1 year). Although the symptoms improved in the majority of caregivers, there was a subset (16%) in whom depression was stable over time.
Cautions: Owing to the study design, there was no control group or any assessment of mental health in the family members before critical illness occurred; thus, causation cannot be established. Moreover, although the observations are both interesting and important, the implications of the findings in terms of management remain unclear. Future studies could focus on interventions for various providers, reversibility of depressive symptoms, and the potential effects of improved family dynamics and well-being on long-term recovery of ICU patients.
Implications: Clinicians should be aware of the high prevalence of depressive symptoms among family members of ICU patients. These symptoms persist over time, and in some cases improvement in symptoms is minimal. Social support of patients and their families during and after critical illness seems appropriate.

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