SYSTEMATIC REVIEW

OPEN

Major Publications in the Critical Care Pharmacotherapy Literature: 2022

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OBJECTIVES: A number of trials related to critical care pharmacotherapy were published in 2022. We aimed to summarize the most influential publications related to the pharmacotherapeutic care of critically ill patients in 2022.

DATA SOURCES: PubMed/Medical Literature Analysis and Retrieval System Online and the Clinical Pharmacy and Pharmacology Pharmacotherapy Literature Update.

STUDY SELECTION: Randomized controlled trials, prospective studies, or systematic review/meta-analyses of adult critically ill patients assessing a pharmacotherapeutic intervention and reporting clinical endpoints published between January 1, 2022, and December 31, 2022, were included in this article.

DATA EXTRACTION: Articles from a systematic search and the Clinical Pharmacy and Pharmacology Pharmacotherapy Literature Update were included and stratified into clinical domains based upon consistent themes. Consensus was obtained on the most influential publication within each clinical domain utilizing an a priori defined three-round modified Delphi process with the following considerations: 1) overall contribution to scientific knowledge and 2) novelty to the literature.

DATA SYNTHESIS: The systematic search and Clinical Pharmacy and Pharmacology Pharmacotherapy Literature Update yielded a total of 704 articles, of which 660 were excluded. The remaining 44 articles were stratified into the following clinical domains: emergency/neurology, cardiovascular, gastroenterology/fluids/nutrition, hematology, infectious diseases/immunomodulation, and endocrine/metabolic. The final article selected from each clinical domain was summarized following a three-round modified Delphi process and included three randomized controlled trials and three systematic review/meta-analyses. Article topics summarized included dexmedetomidine versus other sedatives during mechanical ventilation, beta-blocker treatment in the critically ill, restriction of IV fluids in septic shock, venous thromboembolism prophylaxis in critically ill adults, duration of antibiotic therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia, and low-dose methylprednisolone treatment in severe community-acquired pneumonia.

CONCLUSIONS: This concise review provides a perspective on articles published in 2022 that are relevant to the pharmacotherapeutic care of critically ill patients and their potential impact on clinical practice.

KEY WORDS: critical care; critically ill; pharmacotherapy; review; sedation; septic shock

Clinicians face an inherent need to keep abreast with literature and implement evidence-based medicine into practice. However, given the substantial growth in research articles published annually, most are overcome with the sheer volume of publications (1). A meta-epidemiological study demonstrated an explosion in the number of publications in the field of critical care, concluding the number of publications exceeds the number that can be read (2). To

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KEY POINTS

Question: What were the most influential publications related to the pharmacotherapeutic care of critically ill patients in 2022?

Findings: This systematic search and modified Delphi process revealed three randomized controlled trials and three systematic review/meta-analyses. Article topics included a broad range of critical care topics stratified across various clinical domains including emergency/neurology, cardiovascular, gastroenterology/fluids/nutrition, hematology, infectious diseases/immunomodulation, and endocrine/metabolic.

Meaning: There has been substantial growth in the number of research articles published within the field of critical care annually. This concise review provides a perspective on articles published in 2022 that are relevant to the pharmacotherapeutic care of critically ill patients and their potential impact on clinical practice.

mitigate information overload, strategies have been used to keep up with literature including journal surveillance, interaction with scientific and media communities, and services to journals including article review and editorial work (3). The Clinical Pharmacy and Pharmacology Literature Update (CPPLU) working group within the Society of Critical Care Medicine reviews major critical care journals, distributes a monthly summary to various sections of the Society, and reviews influential articles relevant to critical care pharmacotherapy annually (4–13). Therefore, we aimed to summarize the most influential publications related to the pharmacotherapeutic care of critically ill patients in 2022.

METHODS

A systematic search was conducted of PubMed/Medical Literature Analysis and Retrieval System Online from January 1, 2022, to December 31, 2022, to capture relevant articles related to the pharmacotherapeutic care of critically ill patients. Search criteria consistent with previous reviews are located in **Appendix 1**. Resulting articles were reviewed by two independent authors (P.K.G., P.M.W.) to assess eligibility for inclusion in the full-text review. A full-text review was performed to exclude any remaining articles that did not fulfill inclusion criteria including randomized controlled trial (RCT), prospective study, or systematic review/meta-analysis design, critically ill adult patient population, assessment of a pharmacotherapeutic intervention, and reporting of clinical endpoints. Eligible articles were categorized into clinical domains based upon a consistent theme and entered into a survey (**Supplemental File**, http://links.lww.com/CCX/B252).

An a priori defined three-round Delphi survey was performed to form consensus on influential publications relevant to the pharmacotherapeutic care of critically ill patients. The survey included the article title within each domain and full-text file to assist with ranking. A multiprofessional panel of authors (n = 15) independently ranked articles "within" each clinical domain in terms of overall contribution to scientific knowledge (morbidity/expense) and novelty to the literature. Each round of the Delphi process terminated if an 80% consensus was obtained in any clinical domain. If an 80% consensus was not obtained, articles with less than 50% agreement were removed and the remaining entered into the subsequent round. At the end of the third round, the article achieving the highest consensus agreement was included in this review. Each article selected was summarized including an analysis and applicability to critical care practice.

RESULTS

The systematic search and CPPLU revealed a total of 704 articles, of which 627 were excluded based upon aforementioned criteria, and 33 were excluded following full-text review. The remaining 44 articles were included in the modified Delphi process (**Fig. 1**; and Supplemental File, http://links.lww.com/CCX/B252). No article met the prespecified 80% or more consensus agreement in any round, and therefore, all articles were included in the a priori defined three-round Delphi process. At the completion of three rounds, one article from each clinical domain, achieved consensus agreement and were included in this review.

DISCUSSION

Neurology/Emergency

Dexmedetomidine Versus Other Sedatives in Critically Ill Mechanically Ventilated Adults: A Systematic Review and Meta-Analysis of Randomized Trials. This systematic review and meta-analysis (SRMA) of

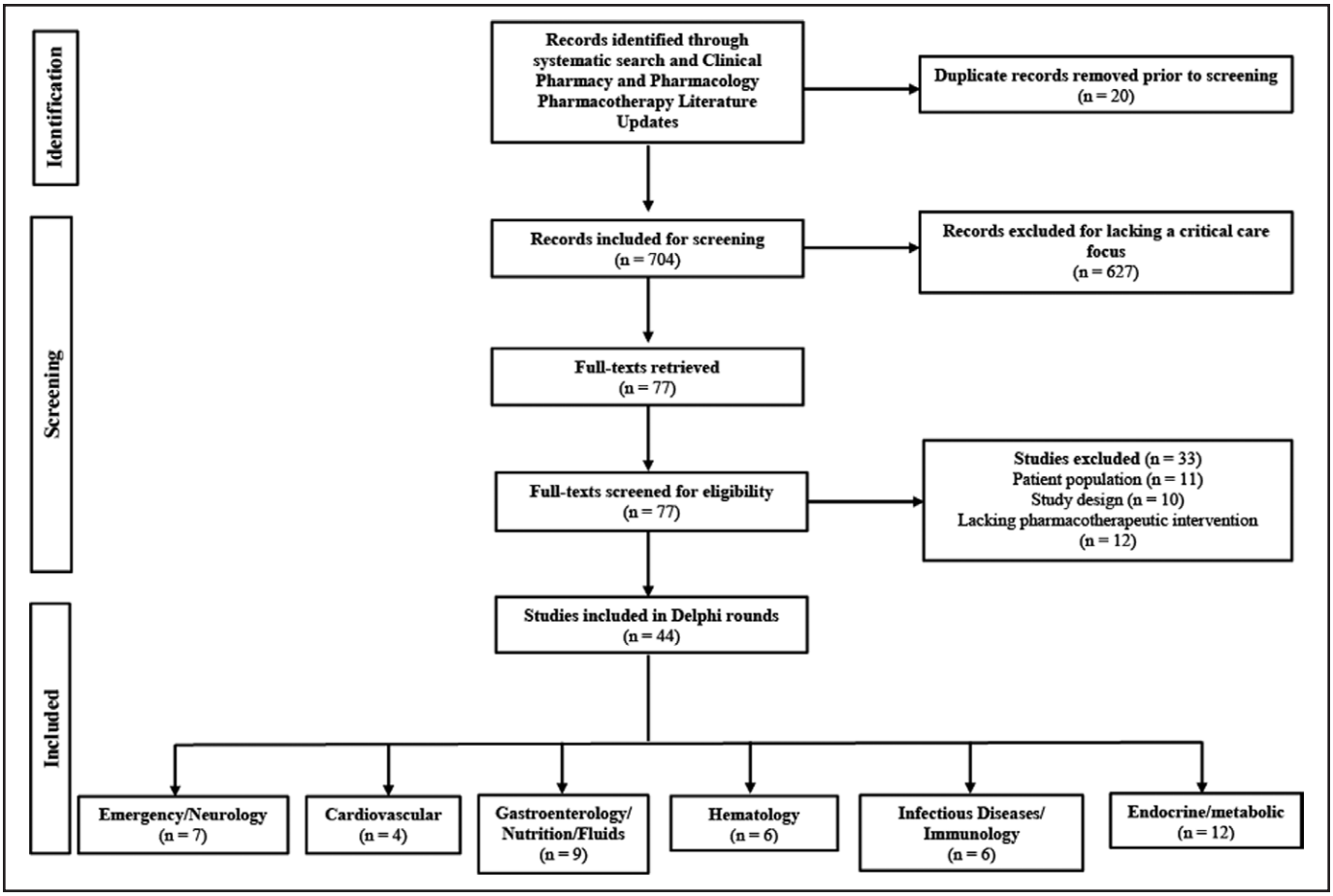

Figure 1. Flow diagram of article screening.

77 RCTs (*n* = 11,997) evaluated the efficacy and safety of dexmedetomidine versus other sedatives in mechanically ventilated adults in the ICU and found a significant reduction in the risk of delirium (relative risk [RR], 0.67; CI, 0.55–0.81), duration of mechanical ventilation (MV) (median difference [MD], –1.8 hr; 95% CI, –2.89 to –0.71 hr), and ICU length of stay (LOS) (MD, –0.32 d; 95% CI, –0.42 to –0.22 d) with dexmedetomidine use compared with other sedatives (14). Patients receiving dexmedetomidine were more likely to maintain lighter levels of sedation with an increased proportion of time spent at their target sedation goal (MD, 3.67 percentage points; 95% CI, 0.98–6.36). Dexmedetomidine was not found to reduce the risk of death at 30 days compared with other sedatives (RR, 0.94; 95% CI, 0.80–1.11) or hospital LOS (MD, –0.10 d; 95% CI, –0.72 to 0.91 d). In the safety analysis, dexmedetomidine increased the risk of bradycardia (RR, 2.39; 95% CI, 1.82–3.13) and hypotension (RR, 1.32; 95% CI, 1.07–1.63); there was not an increased need for interventions related to these adverse effects.

Delirium is prevalent in ICU patients and associated with an increased risk of morbidity and mortality (15). Adherence to the "A2F bundle," including appropriate choice of sedation, increases delirium-free days, and reduces the risk of in-hospital mortality (16). Benzodiazepines are not recommended as first-line for sedation; however, the delirium risk with alternative sedatives remains unclear. In this SRMA, dexmedetomidine reduced the risk of delirium compared with benzodiazepines, propofol, and opioids, with an absolute risk reduction of 11% or number needed to treat of 23 (14). The proposed benefit of dexmedetomidine on delirium may include improved analgesia through central α2 agonism, attenuation of neuroinflammation, improved sleep quality, and facilitation of lighter sedation, thereby enhancing patient communication and interaction (17–19). Although a dose-response relationship could not be elicited from this study, most of the studies included limited doses to less than 0.7 μg/kg/hr with a significant reduction in the risk of delirium at these lower

doses as compared with benzodiazepines, propofol, and opioids (RR, 0.46; CI, 0.34–0.62). Consistent with findings from the Sedation Practice in Intensive Care Evaluation III trial, a lower risk of delirium and duration of MV was demonstrated when dexmedetomidine initiation was within 12 hours of ICU admission (20). Of note, a subgroup analysis by duration of dexmedetomidine noted a shorter duration of use (≤ 24 hr) was associated with the largest reduction in delirium as compared with a longer duration of use (> 24 hr). This is relevant given the potential for tachyphylaxis with prolonged administration. While several studies used a bolus prior to infusion initiation, this strategy is not performed in clinical practice due to the risk of adverse effects. Low baseline mean arterial pressure (MAP), higher Acute Physiology and Chronic Health Evaluation (APACHE) II score, and history of coronary artery disease may increase the risk of hypotension; patient-specific factors should be considered prior to initiation (21).

Strengths of this SRMA included no correlation demonstrated between age and treatment effect, and increasing baseline APACHE II score and escalating doses of dexmedetomidine were associated with lower relative reductions in delirium. In addition, patients in medical, surgical, cardiovascular, and mixed medical/surgical ICUs were included; however, patients with alcohol withdrawal, requiring sedation for shivering, or deep sedation were excluded, thereby limiting the generalizability. A subgroup analysis by dose of dexmedetomidine was unable to be completed as no trial exclusively used doses greater than 0.7 μg/kg/hr. Last, significant heterogeneity in the reporting of results and a lack of individual patient data diminished predefined analyses to determine whether certain baseline factors influenced treatment effect (14).

Collectively, evidence suggests dexmedetomidine reduces the risk of delirium, ICU LOS, and increases liberation from the ventilator, especially when used for less than 24 hours. However, use may be limited by bradycardia and hypotension, with close monitoring required during treatment initiation and dose titration.

Cardiovascular

Beta-Blocker Treatment in the Critically Ill: A Systematic Review and Meta-Analysis. This SRMA of 16 RCTs (n = 2,410) evaluated the effect of β-blockers in critically ill patients (22). Studies including patients with sepsis/septic shock, any form of circulatory failure, burns (> 30% total body surface area), major trauma, and traumatic brain injury (TBI) were included. Eleven quantitative trials (n = 2,103) demonstrated a significant mortality reduction in patients treated with β-blockers compared with placebo or standard of care (SOC) (RR, 0.65; 95% CI, 0.53–0.79; $p < 0.0001$; $I^2 = 0\%$; high certainty of evidence). When separated into short-term (< 14 d) and long-term (> 14 d) mortality, only a significant reduction in long-term mortality with β-blockers was noted (RR, 0.60; 95% CI, 0.48–0.74; $p < 0.00001$; $I^2 = 0\%$; high certainty of evidence). Of the planned secondary endpoints, there was a significant reduction in heart rate (HR) with β-blocker treatment compared with control or SOC (MD at 24 hr, −11.96 beats/min; 95% CI, −20.86 to −3.06; $p = 0.008$; $I^2 = 91\%$ and MD at 48 hr, −13.66 beats/min; 95% CI, −26.10 to −1.22; $p = 0.03$; $I^2 = 93\%$; moderate certainty of evidence) and no difference in vasopressor requirements and MAP between groups (high certainty of evidence). Although the effect on HR reduction is expected, additional patient-centered outcomes such as organ dysfunction and quality of life cannot be inferred from this surrogate endpoint. Endpoints, such as ejection fraction and lactate, were unable to be assessed due to heterogeneity of outcome reporting.

β-blockers are ubiquitously used in a variety of disease states but often avoided in critically ill patients due to negative inotropic, chronotropic, and blood pressure (BP) lowering effects, potentially compromising organ perfusion. It has been hypothesized, however, that β-blockers blunt the adrenergic response and may improve outcomes despite lowering of BP (23, 24). β-blockers, specifically propranolol, have been shown to improve survival in TBI (25). A previous meta-analysis, focusing on the addition of an esmolol infusion in septic patients, demonstrated improved survival (RR, 2.06; 95% CI, 1.52–2.79; p = 0.006) with a 31.1% absolute reduction in mortality (26, 27). Conversely, a cohort of general ICU patients found no association between β-blockers and mortality (adjusted odds ratio [aOR], 1.56; 95% CI, 0.83–2.9; p = 0.16); however, when analyzing patients without diabetes only, an increased association with β-blockers and ICU mortality was demonstrated (aOR, 2.93; 95% CI, 1.19–7.23). This finding of an increase in mortality

with β-blocker use in patients without diabetes should be interpreted with caution given the retrospective nature of this study and post hoc study design (28).

While this is the first SRMA of RCTs on β-blockers in various critically ill patients, the conclusion is limited by small sample sizes and quality of RCTs included, qualitative heterogeneity of β-blockers and endpoints studied and inclusion criteria, and lack of reporting of other hemodynamically active drugs (nonstudy β-blockers).

Based on the evidence, considerable variation remains on the optimal timing of initiation, withholding, and restarting of β-blocker therapy in critically ill patients (29). In addition, choice of agent, patient selection, and optimal hemodynamic targets remain unanswered warranting further research. Therefore, initiation of β-blockers in the ICU with careful monitoring for bradycardia and hypotension should be determined on a case-by-case basis.

Gastroenterology/Fluids/Nutrition

Restriction of IV Fluid in ICU Patients With Septic Shock. The Conservative versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care (CLASSIC) trial was an international, open-label, randomized trial evaluating the restriction of fluids on mortality and serious adverse events in adult patients with septic shock (30). Patients were included if the onset of shock was within 12 hours of screening and received at least 1 L of IV fluids (IVFs) within 24 hours of screening. The restrictive fluid (RF) group (n = 764) could have received fluids for any of the following conditions: severe hypoperfusion (lactate ≥ 4 mmol/L, MAP < 50 mm Hg despite vasopressor or inotropic support, mottling beyond the edge of the kneecap, or urinary output < 0.1 mL/kg/hr during the first 2 hr after randomization), to replace documented fluid losses, to correct hydration or electrolyte deficiency if the enteral route was contraindicated, or to ensure a total daily fluid intake of 1 L. The standard fluid (SF) group (n = 781) had no set limit on the amount of IVF administration and fluids could have been administered for any of the following conditions: fluids given as long as the patient had an improvement in hemodynamic factors, fluids to replace expected or observed losses or to correct dehydration or electrolyte derangements, or maintenance fluid per ICU protocol. Enteral and oral fluids, enteral or parenteral nutrition, and fluids used as a carrier for medication administration were allowed in both groups. Patients in both intervention groups remained in the ICU for a median of 5 days. In the ICU, the RF group received a median 1,798 mL of IVFs compared with 3,811 mL in the SF group, excluding fluids administered with medication and nutrition, during the 90-day trial period. There was no difference in 90-day mortality in the RF group compared with the SF group (42.3% vs 42.1%; 95% CI, –4.7 to 4.9; p = 0.96). Secondary outcomes were not significantly different, including serious adverse events, number of days alive without life support, and days alive and out of the hospital at 90 days.

The findings of the CLASSIC trial are in contrast to previous studies demonstrating higher volumes of IVF to be associated with worsening kidney injury, respiratory failure, and mortality in patients with septic shock (31–33). Nevertheless, comparison of the CLASSIC trial to previous studies is limited given differences in study design, patient severity of illness, sources of infection, and fluid protocols. Hjortrup et al (34) demonstrated that a RF group had a lower mean resuscitation fluid volume (MD, –1.2 L; 95% CI, –2.0 to –0.4 L) at day 5 compared with the standard care group (MD, –1.4 L; 95% CI, –2.4 to –0.4 L) with the higher resuscitation volumes associated with worsening acute kidney injury (odds ratio [OR], 0.46; 95% CI, 0.23–0.92; p = 0.03); however, interpretation of this study was limited by major protocol violations occurring in 37% of patients in the RF group. The findings of the CLASSIC trial are consistent with the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis trial which demonstrated no difference in mortality before discharge home by day 90 with a RF strategy compared with a liberal fluid (LF) strategy (35).

Strengths of the CLASSIC trial include a relatively large sample size and randomized study design. However, the study was unblinded and did not provide data on tools used to guide fluid administration. Additionally, patients received fluids prior to enrollment, with the majority of fluids administered outside the study protocol (e.g., blood products, IVFs from with medication and nutrition, and oral intake), which may have impacted the results. Finally, the 7% absolute difference in 90-day mortality between groups may be considered quite large (36).

Based on the available literature, clinical equipoise exists regarding a RF versus LF volume approach in

sepsis. The current evidence leaves many questions regarding the optimal volume of initial (within the first 24 hr) fluid resuscitation, the effect of additional resuscitation on targets other than MAP and lactate and its associated outcomes, which patient populations would benefit most from a RF versus LF strategy, and when fluid deresuscitation be implemented (37). Therefore, future studies should not only aim to assess the impact of all IVFs administered on mortality and other outcomes but also address these questions.

Hematology

Venous Thromboembolism Prophylaxis in Critically Ill Adults: A Systematic Review and Network Meta-Analysis. This systematic review and network meta-analysis of 13 RCTs from inception to January 2021 (n = 9,619) evaluated: 1) the efficacy of pharmacologic thromboprophylaxis with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH), 2) mechanical thromboprophylaxis, 3) a combination of pharmacologic and mechanical thromboprophylaxis, 4) placebo, or 5) no thromboprophylaxis in adult critically ill patients (38). A majority of patients included were from mixed medical/surgical and trauma ICUs. LMWH prophylaxis reduced the incidence of deep vein thrombosis (DVT) compared with UFH prophylaxis (OR, 0.72; 95% credible interval [CrI], 0.46–0.98; moderate certainty) or control (OR, 0.59; 95% CrI, 0.33–0.90; high certainty) and UFH prophylaxis may reduce the incidence of DVT (OR, 0.82; 95% CrI, 0.47–1.37; low certainty) compared with control. Furthermore, LMWH prophylaxis may reduce the incidence of pulmonary embolism (PE) (OR, 0.47; 95% CrI, 0.03–3.91; low certainty) compared with control; however, the effect of UFH prophylaxis on PE and LMWH prophylaxis compared with UFH prophylaxis on PE was uncertain (OR, 0.70; 95% CrI, 0.05–7.95; low-certainty and OR, 0.65; 95% CrI, 0.08–3.65, respectively). Compared with control, both LMWH prophylaxis (OR, 0.63; 95% CrI, 0.18–1.59; low certainty) and UFH prophylaxis (OR, 0.79; 95% CrI, 0.22–2.28; low certainty) may reduce the incidence of any venous thromboembolism (VTE) defined as any upper or lower extremity DVT or any segmental or proximal PE. Data were insufficient to perform a network meta-analysis for several secondary outcomes including major bleeding, heparin-induced thrombocytopenia, ICU LOS, and mortality.

The rate of VTE varies greatly among patients in the ICU, with the highest rates reported in surgical or trauma patients (39). Thromboembolism prophylaxis is a foundational intervention in critically ill patients (40). VTE is associated with increased healthcare costs and mortality (41). This systematic review has limitations, including a lack of standardized screening protocols to identify DVTs; therefore, the effect of these modalities on clinically significant DVTs is uncertain. Additionally, a majority of patients analyzed were from a mixed medical/surgical and trauma population, thereby limiting generalizability to strictly medical patients. Finally, doses of pharmacological VTE prophylaxis were not standardized, limiting any conclusion of the impact of drug dose on efficacy.

Overall, while this analysis suggests LMWH may be preferable over UFH in reducing the incidence of DVT, caution should be exercised in generalizing these results to patients with concern for bleeding or impaired renal function (creatinine clearance < 30 mL/min). In addition, given the low certainty of evidence for reducing the incidence of PE and effect of these agents on major bleeding, further studies are warranted.

Infectious Disease/Immunomodulation

Comparison of 8 Versus 15 Days of Antibiotic Therapy for Pseudomonas aeruginosa Ventilator-Associated Pneumonia in Adults: A Randomized, Controlled, Open-Label Trial. The Impact of the Duration of Antibiotics on clinical events in Patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia (iDIAPASON) study was a randomized, open-label, noninferiority trial evaluating short duration (8 d) versus prolonged antibiotic therapy (15 d) in adult patients with documented ventilator-associated pneumonia (VAP) caused by *P. aeruginosa* (PsA) (42). Patients were excluded if PsA was isolated from respiratory cultures prior to the current hospitalization, pregnancy, receiving immunosuppression (HIV, immunosuppressive therapy, corticosteroids > 0.5 mg/kg/d for > 1 mo), chronic pulmonary colonization with PsA or bronchiectasis, or received antibiotic therapy active against PsA for an extrapulmonary infection. Antibiotic therapy was initiated following respiratory sampling and choice of therapy was left to the discretion of the treating physician. The primary outcome of PsA recurrence occurring during the ICU

stay until day 90 was defined by a post hoc diagnosis as clinical suspicion of VAP after greater than or equal to 48 hours without effective antibiotic therapy for PsA with fever greater than 38.5°C, leukocytosis greater than 10^9/L or leukopenia less than 4.10^8/L, purulent tracheobronchial secretions, and a new or persistent infiltrate on chest radiograph, then confirmed with a positive quantitative culture. The study was stopped early due to low enrollment and did not include the prespecified number of patients needed to meet statistical power. In the intention-to-treat group, 25 patients (25.5%) in the 15-day group and 31 patients (35.2%) in the 8-day group had a VAP recurrence or were dead in the ICU at 90 days. Noninferiority was not demonstrated as the upper bound of the 90% CI was greater than the predefined criteria of 10% (difference, 9.7%; 90% CI, –1.9% to 21.2%). Similar results were observed in the per protocol group and post hoc adjusted analyses. Furthermore, a higher rate of recurrence was observed in the 8-day group compared with the 15-day group (17% vs 9.2%; difference, 7.9%; 90% CI, –0.5% to 16.8%). There were no differences between groups in duration of MV, ICU LOS, and acquisition of multidrug-resistant organisms.

VAP is a major cause of morbidity and mortality in critically ill patients. While guidelines exist for management of VAP, there continue to be uncertainties regarding optimal treatment duration of VAP caused by PsA (43). This study was consistent in methodology and findings compared with the Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults trial (44). Subsequent trials, however, evaluated treatment duration with conflicting results (45–47).

The iDIAPASON study was strengthened by inclusion of infections only caused by PsA, relatively long 90-day outcomes assessment (minimizing the impact of a differential time of follow-up due to one group receiving a longer duration of therapy), and a standardized definition of recurrence. However, this trial was limited by the open-label design, inability to meet the predefined sample size, and exclusion criteria limiting generalizability of the results.

Notably, while this trial suggested an increased risk of recurrence of PsA-VAP with 8 days of therapy, it remains unknown if a short or long duration should be used; therefore, clinicians should individualize PsA-VAP treatment duration based on clinical response.

Endocrine/Metabolic

Low-Dose Methylprednisolone Treatment in Critically Ill Patients With Severe Community-Acquired Pneumonia. Methylprednisolone in Hospitalized Veterans with Severe Community-Acquired Pneumonia (ESCAPe) was a multicenter, double-blind, RCT evaluating the effects of methylprednisolone on all-cause mortality and secondary endpoints of morbidity and mortality in patients with severe community-acquired pneumonia (CAP) admitted to the ICU within 72–96 hours of hospital presentation from January 2012 to April 2016 (48). A total of 584 patients were randomized 1:1 to receive methylprednisolone (IV loading dose of 40 mg on day 0 followed by a continuous infusion of 40 mg/d on days 1–7, 20 mg/d on days 8–14, 12 mg/d on days 15–17, and 4 mg/d on days 18–20) (n = 297) or placebo (n = 287). The study drug was administered by continuous infusion during the ICU stay and changed to bid via the enteral or IV route after ICU discharge. Of note, 34% of patients met healthcare-associated pneumonia (HCAP) criteria, 11% had acute respiratory distress syndrome (ARDS), and 33% of patients received MV at enrollment. There was no difference in 60-day all-cause mortality between groups (16% vs 18%; OR, 0.89; 95% CI, 0.58–1.38; p = 0.61), 180-day (21% vs 24%; OR, 0.86; 95% CI, 0.58–1.29; p = 1.00) or 1-year all-cause mortality (30% vs 33%; OR, 0.88; 95% CI, 0.61–1.27; p = 1.00). No difference in 60-day mortality was found when adjusted for site and MV (aOR, 0.90; 95% CI, 0.57–1.40; p = 0.63) and baseline patient characteristics (aOR, 0.87; 95% CI, 0.53–1.42; p = 0.58). Additionally, there were no significant differences between groups in the median MV-free days up to day 8 or 28, development of ARDS or vasopressor dependent shock, ICU and hospital LOS, or hospital mortality. In patients receiving MV at randomization, there was a 3-day reduction in duration of MV (median 4 vs 7 d; HR, 1.44; CI, 1.04–1.99; p = 0.21) in the methylprednisolone group.

Benefits to the use of glucocorticoids in CAP include a reduction in need for MV, progression to ARDS, and time to clinical stability, at the expense of hyperglycemia and secondary infection (49). Torres et al (50) demonstrated that use of methylprednisolone in patients with severe CAP and high initial inflammatory response resulted in a decrease in radiographic progression and

decreased treatment failure. The Community-Acquired Pneumonia: Evaluation of Corticosteroids trial concluded ICU patients with severe CAP receiving hydrocortisone had a lower risk of death at 28 days versus placebo with a similar incidence of hospital-acquired infections and gastrointestinal bleeding (51). Of note, patients with a lower acuity were included in these trials as compared with the ESCAPe trial.

Although prior analyses have suggested a mortality benefit with glucocorticoids, significant heterogeneity exists in both the study quality and definition of severe CAP used (52–54). The 2019 CAP guidelines recommend against the routine use of glucocorticoids in CAP, with a higher quality of evidence against its use in nonsevere CAP (55).

Several strengths of the ESCAPe trial include a large population and long-term follow-up. However, interpretation of trial findings is limited by low-recruitment and generalizability given the inclusion of HCAP patients, selection bias as patients were excluded at the discretion of the physician, baseline comorbidities/severity scores, and racial, gender, and age composition of the Veterans Affairs population as compared with the general population. In addition, in-hospital adverse events related to study treatment such as hyperglycemia and gastrointestinal bleeding were not reported in the trial. The lack of benefit may be a result of low doses used or delayed timing of administration (72–96 hr after hospital admission) leading to an inadequate anti-inflammatory response. Nevertheless, a variable response to glucocorticoid treatment in CAP are likely multifactorial (e.g., different agent, dosing, route, duration). Therefore, the use of steroids in ICU patients with severe CAP should be individualized.

CONCLUSIONS

This concise review provides perspective on articles relevant to the pharmacotherapeutic care of critically ill patients. The studies included in this review add to the current body of critical care literature on pharmacotherapy interventions in the ICU and provide insight on areas of future research.

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The content of this article contains previously peer-reviewed and published literature and not original data.

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APPENDIX 1

Search terms: ((((critical care[MeSH Terms]) OR (intensive care[MeSH Terms])) OR (intensive care unit[MeSH Terms])) OR (critical illness[MeSH Terms])) OR (critically ill[MeSH Terms]).

Filters: Full text, Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Meta-Analysis, Pragmatic Clinical Trial, Randomized Controlled Trial, Validation Study.