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Major publications in the critical care pharmacotherapy literature: January–December 2017

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ABSTRACT

Purpose: To summarize selected meta-analyses and trials related to critical care pharmacotherapy published in 2017. The Critical Care Pharmacotherapy Literature Update (CCPLU) Group screened 32 journals monthly for impactful articles and reviewed 115 during 2017. Two meta-analyses and eight original research trials were reviewed here from those included in the monthly CCPLU. Meta-analyses on early, goal-directed therapy for septic shock and statin therapy for acute respiratory distress syndrome were summarized. Original research trials that were included evaluate thrombolytic therapy in severe stroke, hyperoxia and hypertonic saline in septic shock, intraoperative ketamine for prevention of post-operative delirium, intravenous ketorolac dosing regimens for acute pain, angiotensin II for vasodilatory shock, dabigatran reversal with idarucizumab, bivalirudin versus heparin monotherapy for myocardial infarction, and balanced crystalloids versus saline fluid resuscitation.
Conclusion: This clinical review provides perspectives on impactful critical care pharmacotherapy publications in 2017.

Contents

Abbreviations: AII, angiotensin II; ACT, activated clotting time; aPTT, activated partial-thromboplastin time; ARDS, acute respiratory distress syndrome; BARC, Bleeding Academic Research Consortium; dTT, dilute thrombin time; ECT, ecarin clotting time; EHR, electronic health record; MAKE30, major adverse kidney event within the first 30 days after enrollment; mRS, modified Rankin Scale; SAE, serious adverse events; UC, usual care; VFD, ventilator free days.

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1. Introduction

Multiple strategies exist for critical care clinicians to remain well-informed of impactful medical literature, including newsletters, social media and blogs, electronic tables of contents, and critically reviewed article summaries [1]. Internists spend an average of slightly over 4 h each week reading medical literature, [2] suggesting this activity is valued but limits exist on the time able to be allotted to this form of professional development. With the growth in articles published in critical care and intensive care medicine each year, creative methods have been developed to streamline the process of gathering and learning from current medical literature.

Beginning in 2009, the Clinical Pharmacy and Pharmacology Section's Research Committee within the Society of Critical Care Medicine empowered a working group to develop a process for updating its members on recent additions to the critical care and intensive care medicine literature. This process formally resulted in the development of the Critical Care Pharmacotherapy Literature Update (CCPLU) series, which is an accumulation of articles that have been critically reviewed and summarized by critical care and emergency medicine pharmacists. Articles are systematically chosen from 32 journals relevant to critical care practice based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system to assess quality of evidence and strength of recommendations alongside their relevance to clinical practice [3]. Currently, the CCPLU is internationally distributed monthly to an electronic mailing group and through social media networks. Previous annual reviews have been published from our group [4-8]. One-hundred fifteen articles were reviewed in 2017, and two meta-analyses and eight original research trials were included in this review based on their GRADE criteria (highly-rated [1A]), pharmacotherapeutic focus, and expected influence on critical care practice [9-18]. GRADE criteria scores were independently determined by two co-authors. No discrepancies existed.

1.1. PRISM Investigators. Early, goal-directed therapy for septic shock – a patient-level meta-analysis [9]

The Early, Goal-Directed Therapy for Septic Shock—A Patient-Level Meta-Analysis (PRISM) study was a meta-analysis of three government-funded, multicenter, randomized, controlled trials to determine if early, goal-directed therapy (EGDT) improves patient outcomes in adults with septic shock. PRISM included the Protocolized Care for Early Septic Shock (ProCESS), [19] Australasian Resuscitation in Sepsis Evaluation (ARISE), [20] and the Protocolised Management in Sepsis (ProMISe) trials [21].

The ProCESS, ARISE, and ProMISe trials were based on a single-center trial that led to the development of EGDT [22]. Each individual trial failed to show lower mortality with EGDT compared to usual care (UC). This heterogeneous, prospective meta-analysis combined pooled patient-level data from the three trials to determine the effect of EGDT versus UC on 90-day mortality and secondary clinical and economic outcomes. Each individual trial had 80 to 90% power to detect an absolute difference in mortality of 6.5 to 8% between groups. Consequently, PRISM had 80% statistical power to detect a 4 to 5% difference in 90-day mortality using a two-sided p-value of 0.05. All analyses were conducted on an intention-to-treat basis. Cost and cost-effectiveness estimates were reported separately for each trial because the interpretation of pooled cost-effectiveness estimates is unclear when drawn from healthcare systems with different cost structures.

In total, 3763 patients were randomized (EGDT = 1871, UC = 1892), 3723 patients were included in the primary analysis (90-day mortality), and 3511 patients were followed up to 1 year. No difference in 90-day mortality was found (EGDT 24.9% vs. UC 25.4%, adjusted odds ratio (OR) 0.97, 95% confidence interval (CI) 0.82–1.14, $p = 0.68$). Patients in the EGDT group experienced a longer mean ICU length of stay (4.9 days vs. 4.5 days, $p = 0.02$) and received longer mean durations of cardiovascular support (1.9 days vs. 1.6 days, $p = 0.01$). No other secondary outcomes differed significantly. Only two of the 16 subgroups produced significant findings: EGDT was associated with higher mortality in patients with severe chronic liver disease (OR 2.51) and lower mortality among those with severe chronic respiratory disease (OR 0.54) compared to cohorts without those comorbid disease states. There were no differences in mortality in higher APACHE II and SOFA score subgroups between the EGDT and UC groups. For all three trials, the average cost up to 90 days was higher with EGDT compared to UC. Quality of life scores were similar between groups. A significant limitation of the PRISM study was un-blinding of study patients in all three trials, which introduced internal and external biases. Additionally, some clinically important subgroups, such as those with preexisting renal dysfunction and those receiving a vasopressor, had small sample sizes limiting statistical power.

Early recognition and advances in care of sepsis and septic shock (including intravenous fluids and antimicrobials) may explain the lack of benefit from EGDT noted in ProCESS, Arise, and ProMISe as well as the PRISM meta-analysis. Unresolved questions remain, including the most effective IV fluid and vasopressor regimens, the role of hemodynamic monitoring, and the appropriate targets for resuscitation in sepsis and septic shock.

1.2. Nagendran et al. Statin therapy for acute respiratory distress syndrome: an individual patient data meta-analysis of randomized clinical trials [10]

There has been longstanding interest in the use of statin therapy for its immunomodulatory effects in acute respiratory distress syndrome (ARDS). A previous meta-analysis indicated that while observational studies suggest a survival benefit associated with statin use in patients

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