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West Middlesex University Hospital

Antibiotic Administration in Sepsis (Adults)

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to an infection [14]. Without timely treatment, sepsis may progress to septic shock. Sepsis is estimated to effect 31.5 million people worldwide annually, resulting in an estimated 5.3 million deaths [7]. The SOAP study in Europe observed an overall hospital mortality of 36% [18].

Timing of Administration

Evidence on the optimal timing of administration of antibiotics in sepsis patients is limited to observational studies. Findings from a retrospective cohort of 28,150 intensive care patients with sepsis or septic shock demonstrated an increase in mortality associated with delayed initiation of antibiotic therapy. In hospital mortality ranged from 32% in patients whom received antibiotics in less than one hour, to 39.6% in those receiving treatment after six hours [6]. A recent retrospective study analysed the relationship between the time to appropriate antibiotic administration in the emergency department triage and subsequent ICU mortality in patients with *S. aureus* infection. It demonstrated that each hour delay in antibiotic administration is associated with an 11% increase in the odds of 30-day mortality [2]. The Surviving Sepsis Campaign guidelines therefore recommend initiating IV antibiotics as soon as possible and within one hour of the recognition of sepsis or septic shock [11]. The Academy of Medical Royal Colleges (AMORC) have also recently issued guidance to help clinicians prioritise management of patients who are critically ill and most likely to benefit from rapid antibiotic treatment. It also allows patients with possible sepsis identified as less severely ill to benefit from a longer period of investigation and more accurate treatment, while reducing the burden of antimicrobial resistance [1].

Empiric Antibiotic Therapy

In patients when the source of infection is known, antibiotic selection should be made according to local antimicrobial guidance [12]. There is however no single empiric antibiotic regime recommended for all sepsis patients where the source of infection is undetermined. Choice of regime should therefore be guided by patient history, potential source of infection, microbial resistance patterns, organ dysfunction and associated drug toxicities. Broad-spectrum intravenous antibiotics should be commenced within one hour and before a pathogen is identified and/or adequate clinical improvement is noted. Empiric antibiotic therapy should be narrowed as soon as a pathogen has been identified and sensitivities are available [11]. A recent systematic review recommends the infusion of anti-pseudomonal beta-lactam antibiotics over at least 3 hours to

sepsis patients in intensive care as results indicate that this may reduce mortality by up to 30% [17]. Furthermore, the BLING-II randomised controlled trial demonstrated that a continuous infusion of beta-lactam antibiotics was associated with similar efficacy as intermittent infusion in patients with severe sepsis [4]. Following the publication of a review of adverse effects by the European Medicines Agency (EMA) in November 2018, administration of fluoroquinolones should be restricted for use in serious, life-threatening bacterial infections only [5]. This recommendation is endorsed by the UK Medicines and Healthcare products Regulatory Agency (MHRA) [11].

Combination Therapy

Data from a retrospective cohort study which compared 1223 propensity matched bacterial septic shock patients treated with either combination or single agents demonstrated that early combination antibiotic therapy was associated with decreased mortality in the intensive care setting [9]. Use of empiric combination antibiotic therapy is endorsed by the Surviving Sepsis Campaign Guidelines which advocate use of two agents of different antimicrobial class aimed in patients with neutropenic sepsis/bacteremia at the most likely pathogens. It however cautions against the routine use of combination therapy for the ongoing treatment of other serious infections without shock [13].

Procalcitonin-Guided Therapy

Use of procalciton as a biomarker for sepsis has garnered interest over the last two decades. While evidence to support its effectiveness in reducing mortality is lacking, serial measures of procalcitonin have shown to be potentially useful in guiding the decision to continue or stop empiric antibiotics thus reducing antibiotic exposure [15, 3]. According to data from a recent meta-analysis among patients with acute respiratory infections (including those resulting in sepsis), procalcitonin-guided therapy was associated with a 2 day reduction in the antibiotic course, a 27% reduction in antibiotic related side-effects, and a 10% reduction in 30 day mortality rate [16]. These conclusions are supported by the recent PROGRESS ((Procalcitonin-guided Antimicrobial Therapy to Reduce Long-Term Sequelae of Infections) trial which compared Procalcitonin-guided therapy with standard therapy. The trial demonstrated Procalcitonin-guided therapy to be effective in reducing infection-associated adverse events and 28-day mortality in hospitalised patients with sepsis [10].

Conclusion

Early administration of broad-spectrum empiric antibiotics is fundamental in the treatment of sepsis or septic shock. Antibiotic therapy should be initiated as soon as possible, the choice of which should take into account patient history, common local pathogens, microbial resistance patterns, and the suspected

source of infection. In line with guideline recommendations, patients should be reviewed on a daily basis and antibiotic de-escalated as soon as possible [13].

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