Review Article

Right first time!

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Abstract: Septic shock is still a lethal disease in intensive care units (ICU). The mortality can exceed 40% even with therapeutic management. The high mortality is clearly associated with the delay of appropriate antimicrobial therapy. Early diagnosis and identification of infectious source is the mainstay of optimal therapeutic management. On the other hand, source control and optimize antibiotic dosing according to pharmacokinetics (PK)/pharmacodynamics (PD) properties of antibiotics and organ dysfunction of patients are required to get the best clinical outcome.

Keywords: Septic shock; antibiotic; pharmacokinetics (PK); pharmacodynamics (PD); de-escalation

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Introduction

Septic shock has been recently defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are accompanied. Patients with septic shock are needed a vasopressor to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia (1). In the United States, the incidence of severe sepsis has been reported over 750,000 per year and the rising incidence were reported (2). In septic shock, underlying circulatory and cellular metabolism abnormalities increase mortality over 40% (3). Despite the lack of data, the incidence, morbidity and mortality are expected higher in developing countries (4).

Appropriate empiric antimicrobial therapy

The well-known risk factors for severe sepsis and septic shock are age, host genetic characteristics, underlying diseases (diabetes mellitus, immunosuppressive diseases, chronic obstructive disease, cancers, etc.) and use of immunosuppressive agents. However, the timeliness of appropriate therapeutic management influences the prognosis in sepsis (3). Early recognition of infectious source and early initiation of appropriate empiric antimicrobial therapy with source control is crucial for decreasing the risk of organ failure (5). The Surviving Sepsis Campaign suggested two "bundles" of care to improve outcome in sepsis and septic shock; initial management bundle in emergency department within 6 hours and accomplished management bundle in intensive care units (ICU) (6). Rivers and colleagues (7) first showed that "early goal directed resuscitation" of patients before admission to the ICU effectively reduces the incidence of multiorgan dysfunction, mortality, and the use of health care resources among patients with severe sepsis or septic shock. However, after 15 years from this original study, the recent trials showed that "early goal directed resuscitation" with routine placement of a central venous catheter, monitoring of mixed venous oxygen saturation and aggressive red cell transfusion were controversial to improve outcomes of patients with septic shock (8). While, early diagnosis of sepsis and initiation of appropriate antibiotics in 1-hour is unchallenged for the patient survival. Because microbial load is the underlying source of shock and the eradication time of the microbial load will determine the survival rate of the patient (9). Therefore, deferral in the initiation of appropriate antimicrobial therapy has great effect on the mortality of patients. In a retrospective cohort study, Kumar *et al.* (10) determined the prevalence and impact on mortality of delays in initiation of effective therapy from

initial onset of recurrent/persistent hypotension of septic shock. They found that administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 80% and in the first 6 hours after hypotension is identified, survival decreases by 7.6% for every deferral hour in antimicrobial administration. On the other hand, in their retrospective study, only 50% of septic shock patients received effective antimicrobial therapy within 6 hours of documented hypotension.

The suspected site of infection, the origin of the infection (i.e., community acquired or healthcare associated), previous use of antimicrobials and drugs, local microbial-susceptibility patterns and patient risk factors for colonization or infection with multidrug-resistant pathogens will determine the choice of empirical therapy. Empirical intravenous antibiotic therapy with optimal dosages should be initiated as soon as possible with the coverage of all possible pathogens (11,12). However, cultures from suspected infectious source, including blood cultures, have to be obtained prior to the initial antibiotic dose. Culture results will figure the rationale antimicrobial strategy. On the other hand, contamination of cultures (i.e., false positive results) or obtaining cultures after antimicrobial therapy (i.e., false negative results) are two major difficulties in the management of antimicrobial therapy (13).

De-escalation therapy

To optimize the empiric antimicrobial therapy, broad spectrum antimicrobials or combination antimicrobial therapy could be used. De-escalation therapy by switching to or interrupting of a drug class resulting in a less broad spectrum coverage is recommended in the management of septic shock (14).

The main advantage of combination therapy is broad spectrum coverage that increases the probability of appropriate initial antimicrobial therapy. On the other hand, reducing the risk for emerging resistance during therapy, potential additive or synergistic effect leading to more rapid pathogen clearance are the other potential advantages. Also, combination therapy has the disadvantages of increased risk for toxicity and bacterial superinfections with resistant pathogens (14). On the other hand, in a meta-analytic/meta-regression study, Kumar and colleagues (15) showed that combination anti-infective therapy reduces mortality in patients with serious bacterial infections at the highest risk for death (>25%) and failed to show benefit of combination therapy in low risk patients for death (<15%). Combination therapy is recommended for neutropenic patients with sepsis, patients with risk factors for multi-drug resistance (MDR) pathogen infections and patients with severe pneumonia (16). In the recent years, MDR is a growing problem in ICU worldwide (17-19). In the era of MDR pathogens, initially appropriate antibiotic therapy is more complicated that causes poor outcome (20-23). Zilberberg *et al*. (24) indicated that MDR pathogen was the strongest predictor of initial inappropriate antibiotic therapy with an excessive impact (13.05-fold) on mortality. Also changing inappropriate antibiotic to appropriate antibiotic after culture results obtained does not reduce the mortality risk of these patients. Identifying high risk patients for MDR infections and coverage of these emerging pathogens in combination therapy can overcome this problem (16).

Broad spectrum empirical monotherapy is also recommended in septic shock to achieve appropriate empiric therapy (1,14,16). A broad spectrum antibiotic can be chosen by the evaluation of primary infectious source, expected susceptibility of the pathogen, previous infection and antibiotic use (14,16). Carbapenems are the most common antibiotics for the broad spectrum coverage (16). De-escalation strategy is safe and significantly associated with lower mortality (12,14,16,25). In one prospective, observational study, in 35% of the patients admitted to the ICU, de-escalation therapy was performed and found as a protective factor for the mortality (26). On the other side, nosocomial infection occurrence is also less often in patients with adequate empiric therapy due to early improvement of sepsis and shortening of length of hospital stay. Consequently, de-escalation of the antimicrobial is recommended to minimize the selection of resistance (13).

Timing of antibiotics

Timely administration of empiric antibiotics is also affect the patient's survival like appropriateness of empiric antibiotics (27). The suggested time for initiating antibiotics is within the first 6 hours and ideally within 1-hour. For each 1-hour delay in the administration of appropriate antibiotic therapy increased mortality and length of stay (14,28). Initiating of antibiotics 8 to 24 hours after diagnosis is defined as delayed antibiotic therapy and in a study it was shown that survival decreased by 7.6% for every 1 hour of

antibiotic delay (10,14).

Source control

Source control is another important issue for the survival of patients. Surgical debridement of necrotizing infections, drainage of abscess or removal of foreign material are the methods for source eradication. Prompt source control within the first 12 hours is recommended, however the patient's clinical status should be weighed for the appropriate timing of source control (1,13). Exceptional of these cases is peripancreatic necrosis that the surgery should be postponed until adequate demarcation area is clearly defined (1).

Pharmacokinetics (PK)/pharmacodynamics (PD) of antibiotics

PK defines the time course of drug concentration in the body as a result of absorption, distribution, and elimination of a drug after administration. On the other hand, PD defines the relationship between drug concentration and its effect at target site (29). To have the optimal results from antibiotic therapy, the PK/PD characteristics of the antibiotics should be taken into consideration for antibiotic dosing. Furthermore, in septic shock patients, PK/PD parameters such as target site penetration, clearance, drug level and volume of distribution (V_d) change that affect the efficacy of antibiotics. In septic shock, endothelial dysfunction and microvascular failure cause impaired target site penetration of antibiotics. Also altered clearance of antibiotics in septic shock patients is associated with therapeutic failure or toxicity. On the other hand, large volume IV fluid resuscitation or endothelial dysfunction and capillary leak due to systemic inflammation may increase V_d. An increased V_d influences hydrophilic antibiotics' (β-lactam antibiotics, aminoglycosides, glycopeptides, lipopeptides) concentration because these antibiotic's tissue distribution is limited to the extracellular space and clearance is mainly by renal mechanism. In contrast, lipophilic antibiotics (fluroquinolones, glycyclines, lincosamides, macrolides, metronidazole, tetracyclines) have a large V_d with greater tissue and intracellular penetration and metabolism is mainly by hepatic mechanism. Also, loading doses (LDs) are important in septic shock patients to achieve therapeutic concentrations and efficient bacterial killing rapidly. Higher initial doses is generally recommended for septic patients and following dosing can then be modified according to organ dysfunction (30,31). These data propose that hydrophilic antibiotics require an increased LD in the severe infections, whereas a LD is not needed in lipophilic agents (16,30,31). Because the LD of any drug is calculated from the V_d and the required plasma concentration (Cp) using the formula LD = V_d × Cp. Both V_d and Cp can be affected by severity of illness (32).

On the other side, antibiotics are classified as time-dependent, concentration-dependent and concentration dependent with time dependence. Beta lactams, carbapenems and linezolid are the most common used antibiotics in septic shock and these antibiotics are time-dependent killing antibiotics. For these antibiotics, the key PK parameter for maximum efficacy is the time that serum levels above the minimal inhibitory concentration (MIC) of the pathogen. Continuous or prolonged infusion is suggested to have the optimal efficacy (improved clinical cure, shorter hospitalization and lower mortality) from beta lactams, carbapenems and linezolid (5,30). Whereas, fluoroquinolones, aminoglycosides, colistin and vancomycin are concentration-dependent antibiotics and high peak drug concentrations are needed for maximal efficacy (5,30). For PF/PD optimization of antibiotics and improved outcome in septic shock patients, therapeutic drug monitoring is suggested for many antibiotics (vancomycin, beta lactams, etc.) (31).

In septic shock patients, organ failure (renal or hepatic) will affect antibiotic clearance or metabolism. Acute renal failure can be frequently seen and renal replacement therapy (RRT) may be needed. RRT can influence drug PK and therapeutic concentrations of antibiotics. The risk of poor outcome due to subtherapeutic concentrations is higher than the risk of toxicity due to organ failure in septic shock patients. On the other hand, subtherapeutic concentrations is a risk for the development of multidrug resistance. Antibiotic dosing should be based on organ failure or support and therapeutic drug monitoring could be used to get the optimal dosing (33).

In conclusion, high mortality in septic shock is clearly associated with the delay of appropriate antimicrobial therapy. Early diagnosis and identification of infectious source is the mainstay of optimal therapeutic management. On the other hand, source control and optimize antibiotic dosing according to PK/PD properties of antibiotics and organ dysfunction of patients are required to get the best clinical outcome.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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