Antimicrobial therapy in patients with septic shock

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Summary
Providing antibiotics is a life-saving intervention in patients with septic shock. Cultures as clinically appropriate before antimicrobial therapy are required. Guidelines recommend providing broad-spectrum antibiotics within the first hour after recognition of shock. The site of infection, the patient's history and clinical status, and the local ecology all affect the choice of empirical treatment. The appropriateness of this choice is an important determinant of patient outcome. At 48-96 h, the antimicrobial treatment should be systematically reassessed based on the clinical course and culture results. Cessation, de-escalation, continuation, or escalation are discussed according to these variables. Unnecessary treatment should be avoided to reduce the emergence of multidrug resistant pathogens.

Method
This article is based on a PubMed search using "sepsis", "empirical", "antibiotics", "de-escalation" and "ICU" as keywords. The search focused on the 2010-2015 period but previous references were added when the authors considered it appropriate, especially for seminal articles. We selected...
Empirical antimicrobial therapy refers to the initiation of treatment before the determination of a firm diagnosis. Generally, this term is used to describe treatment for patients receiving antibiotics before identification of the specific microorganism causing the infection. Inappropriate empirical antimicrobial therapy is defined by the absence of an antimicrobial agent directed against the specific class of microorganisms responsible for the infection and the administration of an antimicrobial agent to which the microorganism responsible for infection is resistant. “Broad spectrum antibiotics” refers to antibiotics with activity against *Pseudomonas aeruginosa* while “broad spectrum antimicrobial therapy” refers to the combination of antibiotics with activity against *P. aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA). A joint task force from the European centre for disease prevention and control and the United States centers for disease control and prevention has defined resistant organisms as follows: a multidrug-resistant organism (MDR) is one with acquired non-susceptibility to at least one agent in three or more antimicrobial categories; an extensively drug-resistant organism (XDR) to at least one agent in all but two or fewer antimicrobial categories, and a pandrug-resistant organism (PDR) to all agents in all antimicrobial categories [6].

**Empirical antimicrobial therapy**

**Principles**

Empirical antimicrobial therapy is used if a suspected severe infection is likely to impair patient outcome. The driving force behind this strategy is the consistent finding that delays in the initiation of appropriate antibiotic therapy in patients with severe infection is associated with increased mortality [2-4]. Patients suspected of having an infection and hemodynamic impairment are candidates for empirical antimicrobial therapy. Such treatment is also required in selected infections such as severe sepsis, meningitis, pneumonia, peritonitis, pylonephritis, and endocarditis, and in specific patient populations (e.g., with neutropenia or splenectomy). Waiting for results of microbiological culture before introducing antibiotics in those specific groups of patients cannot be recommended.

The challenge in the selection of initial empirical therapy is to provide an appropriate therapy without microbiological documentation, given that inappropriate antibiotic therapy is associated with increased mortality in critically ill patients [5]. Adherence to guidelines seems to be associated with an increased rate of appropriate therapy [7,8].

In order to minimize the risk of failure, broad-spectrum antibiotics are typically used. However, this approach results in greater use of antibiotics than decisions based on culture findings [9] and may be associated with the emergence of MDR, *Clostridium difficile* infections, and increased costs. Empirical antibiotic therapy must always be re-assessed at 48-96 h and tailored as soon as cultures and sensitivity profiles become available.

**Best timing for providing an empirical antimicrobial therapy**

For each patient, antimicrobial therapy may be initiated on an emergency, urgent, or delayed basis. Emergency is defined by the need to start antibiotics within 1 h after diagnosis, urgent by the start of antibiotics within 6-8 h after diagnosis, and delayed by the start of antibiotics within 8-24 h after diagnosis. It is critical to underline that the benefit for administering antibiotics within 1 h after shock recognition was not confirmed in a recent systematic review of literature [10]. Whatever the timing of antibiotic initiation, samples including blood cultures are required before the first administration. In a large observational study, obtaining blood cultures before antibiotics were administered was associated with improved survival [11]. Although this result probably reflects good practices, obtaining blood cultures may also serve to refine the treatment after bacteriological results are obtained.

Emergency empirical antimicrobial therapy is required in patients with hemodynamic impairment and suspected infection. Severe sepsis is defined by the association of signs of sepsis and organ dysfunction (cardiovascular, pulmonary, neurologic, and hepatic). Septic shock is defined by the need to introduce vasopressors in a patient with a suspected infection. Several studies of patients with severe sepsis and septic shock have shown that the administration of antibiotics within the first hours after diagnosis is associated with improved survival [2-4,11] despite the findings of the systematic literature review described above [10]. Each hour of delay in antibiotic administration after diagnosis has been associated with an average decrease in survival of 7.6%; every 10-min delay decreases
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Survival by 1% [4]. Thus, guidelines recommend the prompt introduction of antimicrobial therapy in these patients [12]. Bacterial meningitis is another indication for emergency antimicrobial therapy [13]. In a seminal study, an interval between admission and antibiotic therapy longer than 3 h was the strongest predictor of mortality [14]. Sepsis in splenectomized or neutropenic patients should also be treated without delay. After splenectomy, pneumococci account for 50–90% of infections and may be associated with mortality of up to 60% [15]. The most common situation encountered in patients with infection probably involves the need for urgent antibiotic therapy. Progressive change in the clinical picture over several hours indicates the need to initiate antibiotic therapy, as seen frequently in mechanically ventilated patients with fever, whose chest radiography images worsen over the course of a day. Sometimes, other investigations, such as a computed tomography scan or ultrasound may serve to confirm the diagnosis. Gram stain results may facilitate the decision, in view of their excellent negative predictive value [16].

For community-acquired pneumonia, the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines recommend that the first antibiotic dose be given in the emergency department [17]. Empirical antibiotics should be initiated in patients with suspected hospital-acquired pneumonia in the presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever > 38 °C, leukocytosis or leukopenia, and purulent secretions) [18]. Antimicrobial therapy for intra-abdominal infection should be initiated without delay [19]. A common error is to administer antibiotics after the source control in order to collect samples before antimicrobials are administered.

Criteria of choice

A judicious choice of antimicrobial therapy should be based on the host characteristics, site of infection, local ecology, and the pharmacokinetics/pharmacodynamics of the antibiotics. Toxicity and costs should also be considered. As guidelines have specifically described the use of antibiotics in each condition, hereafter, we report only the principles of antibiotic choice.

Host characteristics

Standard risk factors for MDR carriage are antibiotic treatment in the preceding 90 days, a current hospitalization of 5 days or more, a high frequency of antibiotic resistance in either the community or the specific hospital unit, hospitalization of 2 days or more in the preceding 90 days, residence in a nursing home or extended care facility, home infusion therapy, home wound care, a family member with MDR, and immunosuppression [18]. Susception is warranted for travellers coming from – and especially hospitalized in – countries with high incidence of MDR [20].

Site of infection

The site of infection is one of the major determinants in the choice of antibiotics. The respiratory tract (63%), abdomen (20%), bloodstream (15%), and urinary tract (14%) are the most frequent sites reported for ICU infections [1]. For patients without risk factors for MDR carriage, ventilator-associated pneumonia is generally related to Staphylococcus aureus, Haemophilus influenzae, S. pneumoniae, Legionella spp., Mycoplasma pneumoniae, Chlamydia pneumoniae, and viruses [18]. For patients with risk factors for MDR pathogen carriage, P. aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae and MRSA should be suspected [18].

Intra-abdominal infections are generally polymicrobial with Gram-negative bacteria (E. coli, Enterobacter spp. and Klebsiella spp.), Gram-positive bacteria (enterococci in ~20% of the cases) and anaerobes (Bacteroides sp. in ~80% of the cases). For patients with identified risk factors, or those with tertiary intra-abdominal infection, MDR (including P. aeruginosa, A. baumannii and MRSA) and yeasts should be suspected [19]. Skin infections are frequently polymicrobial. Suspected bacteria should be Staphylococcus spp. (40%), S. aureus (30%), anaerobes (30%), and Gram-negative bacteria (10–20%). Bacterial cerebrospinal fluid infections in outpatients are due to S. pneumoniae (35%) and Neisseria meningitidis (32%) [14].

Local ecology

Knowledge of local bacteriologic patterns increases the likelihood of prescribing appropriate antimicrobial therapy. Regular surveillance cultures for guiding empirical therapy are suggested to assess the level of resistance in specific units [21]. Regular culture surveillance is critical for revising local protocols according to local ecology changes. A meta-analysis has shown that surveillance cultures facilitate prediction of MDR [22]. However, they are also time-consuming and costly. Routinely, clinical screening of patients at ICU admission may predict the risk of MDR colonization and thereby avoid the need for systematic surveillance cultures [23]. In addition, the real impact of such systematic cultures on the choice of empirical antibiotics remains uncertain. In contrast, a regular assessment of the local ecology within the ICU is probably important to optimize the success of an empiric antimicrobial therapy [24].

Pharmacokinetics/pharmacodynamics

ICU patients develop pathophysiological changes during their hospitalization that affects the antibiotic pharmacokinetics and thus necessitates adaptation of doses and intervals [25,26]. Volume of distribution and clearance are generally altered. An increase in volume of distribution typically affects hydrophilic antibiotics and may warrant an increase in the initial dosing requirements to achieve the target drug concentrations [26]. Clearance changes affect day-to-day dosing requirements for patients developing very high clearance due to increases in
capillary permeability and the development of "third-spacing" [27]. The disproportionate redistribution of albumin from intravascular to extravascular compartments results in low plasma albumin concentrations and profoundly affects the pharmacokinetics of antibiotics that bind to serum albumin [28]. Pharmacokinetic/pharmacodynamic optimization of antibiotics is a critical tool for improving dosing regimens for ICU patients [26-28]. The bedside variability of patients with sepsis is extreme. Therapeutic drug monitoring is probably the best option for optimizing antibiotic dosage, although strong evidence for this is scarce [29,30]. In a recent survey, therapeutic drug monitoring of vancomycin, piperacillin/tazobactam, and meropenem was used by 74%, 1%, and 2% of the respondents, respectively [31]. For aminoglycosides, which are concentration-dependent, the recommended approach is the use of high once-a-day doses in order to achieve an adequate peak serum concentration. It is strongly recommended to limit prescriptions to 3 days maximum [24]. For beta-lactams, a time-dependent class of antibiotics, the administration of a loading dose followed by a continuous infusion seems the best way to achieve effectiveness [32]. A large randomized clinical trial failed to show a survival benefit with this strategy [33], but a higher rate of clinical cure has been obtained elsewhere [34]. Glycopeptides are also time-dependent. Administration of the drug by continuous infusion is recommended, based on monitoring of plasma concentrations [24].

**Monotherapy versus combination therapy**

Combined antibiotic therapy is widely used in clinical practice and is aimed at widening the spectrum of activity of antimicrobial therapy, increasing bactericidal activity, and preventing the development of resistance. Combination is recommended for patients with septic shock [12]. The impact of combination therapy for infections with Gram-negative bacteria has been evaluated by several studies and summarized in a meta-analysis [35]. The clinical data supporting the superiority of combination therapy versus monotherapy are neither overwhelming nor definitive. The greatest benefit of combination antibiotic therapy is to increase the likelihood of using an effective agent during empiric therapy, rather than exploitation of in vitro synergy or the prevention of resistance during definitive treatment. In contrast, increased toxicity with combination therapy has been well-documented. Due to the increased mortality rate associated with delays in appropriate, effective antimicrobial treatment, initiating a broad-spectrum empirical antimicrobial treatment (which often means combination therapy) at the onset of septic shock seems prudent. A combination of beta-lactam and aminoglycoside should be preferred to that of beta-lactam and fluoroquinolones, even in patients with renal impairment [24,36]. Specific infections may require combination therapy, including, for example, infections in patients with risk factors for MDR. A combination therapy for infections due to carbapenemase-producing *K. pneumoniae* strains seems superior to monotherapy in terms of mortality [37]. Neutropenic patients also require a combination of antibiotics.

**Reassessment of antimicrobial treatment after culture results**

**De-escalation strategy**

Reducing the spectrum and number of antibiotics as soon as the responsible pathogen is identified is, theoretically, an effective method to decrease the exposure of patients to antibiotics [38]. The definition of de-escalation remains matter of debate, although a French study group reached a consensus for a basic definition [39]. An earlier French randomized clinical trial applied a definition making the following changes once the susceptibility and culture results for the suspected causative bacteria were available: switch the "pivotal" antibiotic for empirical treatment to an antibiotic with a spectrum as narrow as possible; stop the companion drug (aminoglycoside or fluoroquinolone or macrolide) on day 3; and stop the empirical antibiotics against MRSA if MRSA was not identified in "microbiological cultures" [40]. This strategy has not negatively impacted outcomes in three observational studies [41-43], although it should be noted that empirical treatment was preferentially de-escalated in patients with an early positive clinical response [43]. Two randomized clinical trials did not confirm these findings [40,44]. In one, de-escalation of antibiotic treatment resulted in prolonging the ICU stay, but the mortality rate was unaffected [40]. Current evidence suggests that de-escalation should depend on the relevance of cultures and clinical course (figure 2). The presumed "positive" impact of de-escalation on local microbial ecology remains to be confirmed in well-conducted studies [38].

**Figure 2**

**Strategy for the decision of de-escalation according to clinical severity and sample quality**

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Shortening the duration of antimicrobial therapy

Excessive treatment duration is probably a major cause of the emergence of MDR pathogens. For ventilator-acquired pneumonia, in the absence of a non-fermenting Gram-negative bacilli infection, a fixed 7- or 8-day course of antibiotic therapy seems adequate [45]. In the presence of such bacilli, a prolonged 12- to 15-day course has been associated with a lower rate of recurrence than the 8-day course [45]. For bloodstream infections, no significant difference in cure or survival was detected for bacteremic patients receiving shorter (5-7 days) versus longer (7-21) therapy [46]. The French guidelines on intra-abdominal infections recommend a duration of 5 to 15 days for postoperative and healthcare-associated infections [19]. Future studies should confirm if short durations are safe in those patients. Short durations have also been suggested for urinary tract infections [47].

Procalcitonin-guided antibiotic discontinuation is a growing field of research. The monitoring of procalcitonin level as a guide to cessation of an antibiotic therapy has been associated with a diminution of antibiotic duration with no effect on mortality [48]. Adherence to this concept should lead to stopping treatment in patients with low procalcitonin levels or significant decreases between two measurements. However, there is a need for evidence supporting this strategy in units with protocols of short-duration antimicrobial therapy. Finally, in patients with negative cultures, antibiotics can probably be stopped safely [49]. Investigations are required to understand the cause of shock.

Specificities of MRSA infections

Vancomycin should be used as first-line therapy in patients with MRSA infection. Administration using bolus and continuous infusion is recommended. The goal is to reach high plasma concentration (> 20 mg/L). Other antibiotics should be discussed based on the assessment of both renal function and the minimal inhibitory concentration. Linezolid is recommended for ventilator-associated pneumonia due to MRSA when the minimal inhibitory concentration for vancomycin is greater than 1 mg/L or renal impairment is present. Daptomycin seems to be an interesting option for treating patients with bacteremia or endocarditis due to MRSA in the same circumstances [24].

Formal protocol based on local ecology

Antimicrobial guidelines, automated antimicrobial utilization guidelines, and protocols are useful tools for ensuring appropriate antibiotic prescription, which in turn reduces the development of MDR [7,50]. Inappropriate treatment of infections is often secondary to absence or violation of protocols [7]. A formalized antibiotic discontinuation policy has reduced the duration of antibiotics and thus may positively affect the antibiotic resistance profile [51]. Hence, policies aiming at limiting antibiotic prescription should be encouraged to reduce the development of antimicrobial resistance [24]. New technology for rapid identification of pathogens should be included in the dynamic strategy [52]. These protocols should include the entire process aiming at reducing antibiotic exposure (table I).

Conclusion

The choice of antibiotics is probably the first determinant of survival in patients with septic shock. An integrative strategy of dynamic management of antimicrobial treatment for septic patients should be supported by written protocols (figure 3). This strategy includes knowledge of local ecology and of the patient’s history and clinical status. Early reassessment is mandatory, based on both the patient’s course and the identification of the pathogen in cultures. Short treatment durations should be the rule for all patients. Efforts are required to avoid excessive antimicrobial utilization for non-life-threatening infections.

Disclosure of interest: M.L. received fees for consulting (Basilea) and educative support (MSD).
B.P., G.D. and C.M. declare that they have no competing interest.

Table I

Reduction of antibiotic exposure

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<td>Restrict antibiotic treatment for documented infections unless life-threatening conditions</td>
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<tr>
<td>Optimize pharmacokinetics/pharmacodynamics</td>
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<td>Use combination therapy only in patients with shock</td>
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<tr>
<td>Reassess continuously the need for antibiotics</td>
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<tr>
<td>Shorten duration of antibiotic treatment</td>
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<tr>
<td>Identify a referent infectious disease specialist in the intensive care unit</td>
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<td>Adhere to your local protocols</td>
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Figure 3

Decision about antimicrobial treatment: interactions between health professionals

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