Antibiotic therapy in patients with septic shock*

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Introduction

Empirical antimicrobial therapy refers to the initiation of treatment prior to determination of a firm diagnosis. It is most often used when antibiotics are given to a patient before the specific micro-organism causing an infection is known. This is always the case in septic shock patients. As stated elsewhere, this therapy ranges from ‘derived from experiment and observation rather than theory’ at one extreme, to ‘relying on medical quackery or uninfluenced by pathology or clinical tools’ at the other. Inappropriate empirical antimicrobial therapy is defined as the absence of antimicrobial agents directed against a specific class of micro-organisms and the administration of an antibiotic to which the micro-organism responsible for infection was resistant. ‘Broad-spectrum antibiotics’ refers to antibiotics with activity against Pseudomonas aeruginosa including imipenem-cilastatin, piperacillin-tazobactam, ceftazidime, or ciprofloxacin. Limited-spectrum antibiotics will only refer to β-lactam antibiotics without activity against P. aeruginosa (essentially, ceftriaxone and amoxicillin-clavulanate).

Principles

The driving force behind this strategy is the consistent finding that delay in the initiation of appropriate antibiotic therapy in patients with severe infection is associated with increased mortality. Patients in whom there is a suspicion of infection and with haemodynamic impairment, for example requiring a fluid challenge or vasopressors, are candidates for receiving empirical antimicrobial therapy. Such treatment is also required in selected infections, for example severe sepsis, meningitis, pneumonia, peritonitis, pyelonephritis or endocarditis, or in specific patient populations (Figure 1). The timing of antibiotic administration is critical, impacting on the outcome (Figure 1). In patients with severe infection, any delay is associated with increased mortality and morbidity and carers should not wait for the results of microbiological culture before introducing antibiotics in these groups of patients.
The selection of initial antibiotic therapy is based on the risk factors for specific pathogens, modified by knowledge of local patterns of antibiotic resistance and organism prevalence. This treatment should be efficient against the bacteria involved in the suspected infection. Indeed, inappropriate empirical antibiotic therapy is widespread and associated with increased mortality in critically ill patients. For instance, increased mortality was seen in patients treated with empirical piperacillin-tazobactam therapy and Pseudomonas aeruginosa bacteremia due to isolates with reduced piperacillin-tazobactam susceptibility. The challenge is to provide an appropriate therapy without any microbiological documentation. In this setting, adherence to guidelines makes it possible to administer empirical antibiotic treatments effective against the most probable pathogens responsible for the potential infection. A recent study showed that adherence to standard operating procedures is associated with a shorter duration of treatment of pneumonia, a shorter duration of mechanical ventilation and a shorter ICU stay.

Barriers to physicians' adherence to guidelines include awareness, familiarity, agreement with the guideline, belief that one can actually perform an appropriate behaviour, outcome expectancy (the expectation that a given behaviour will lead to a particular consequence), the ability to overcome the inertia of previous practice, and the absence of external barriers to follow recommendations. In order to minimize the risk of failure, empirical antimicrobial therapy is typically broad-spectrum. However, the major limitation to this approach is that it consistently leads to more antibiotic therapy than when the decision is based on the results of microbiological cultures. This practice can be associated with the emergence of multi-drug resistant pathogens, infections due to Clostridium difficile, and increased costs. In parallel, as evidence for administering empirical antibiotics is not always found it is important to determine the conditions when antibiotics must, absolutely, be prescribed to a given patient. In all patients, empirical antibiotic regimens should be reassessed and adjusted as soon as culture and sensitivity results become available. This practice, usually implies de-escalation (but sometimes escalation if the pathogens are not covered), is associated with reduced costs, a decreased incidence of super-infection and minimal development of antimicrobial resistance. Candida colonization and invasive candidiasis in ICU is a major nosocomial problem. There is a clear relationship between the use of antibacterial agents and subsequent candida colonization. The consequences of antibiotic overuse are well-described and beyond the scope of this review.

**Timing**

In each patient, the timing of the start of an antibiotic can be considered as emergency, urgent, or delayed (Figure 1). Emergency and urgent are defined by the need for starting antibiotics within 1 hour and within 6-8 hours after diagnosis, respectively. Delayed antibiotic therapy is defined by the start of antibiotics 8 to 24 hours after diagnosis. In patients with severe sepsis or septic shock, observational
studies have shown that the administration of antibiotics within the first hour after diagnosis is associated with improved survival. Each hour of delay in antibiotic administration after diagnosis is associated with an average decrease in survival of 7.6%; thus, every 10 min, survival is decreased by 1%. Current guidelines recommend prompt antimicrobial therapy in these patients.18 Several observational studies have confirmed a strong association between prompt introduction of antibiotics and survival.19-21 They underline the need to provide appropriate antibiotics within the first hour after sepsis identification.22 Inappropriate initial antimicrobial therapy for septic shock occurs in ~ 20% of patients and is associated with a five-fold reduction in survival.

Choice of empirical antimicrobial therapy

A judicious choice of antimicrobial therapy should be based on the host characteristics, the site of infection, the local ecology, and the pharmacokinetics and pharmacodynamics of antibiotics. Toxicity and costs are also considered. The choice between monotherapy and a combination of antibiotics is discussed below. Antimicrobial options for severe nosocomial infections are suggested in Table 1. As guidelines are available which specifically describe the use of antibiotics in each condition, we have only reported the principles of antibiotic choice.

Table 1
Potential bacteria responsible for sepsis depending on the site of infection and suggested antibiotics for use in severe infections. MRSA: methicillin-resistant Staphylococcus aureus; MRP: multi-resistant pathogen. Percentages do not necessarily add up to 100, because patients may have more than one type of infection or micro-organism.

<table>
<thead>
<tr>
<th>Site</th>
<th>Bacteria</th>
<th>%</th>
<th>Suggested treatment</th>
</tr>
</thead>
</table>
| Urinary tract infections (severe acute pyelonephritis) | Enterobacteriaceae including:  
  • Escherichia coli  
  • Pseudomonas aeruginosa  
  • Enterococcus sp.  
  • Staphylococcus sp. | 60-70  
  40  
  8  
  15  
  4 | Ceftriaxone IV or ceftazidime (if suspicion of P. aeruginosa)  
  ± aminoglycoside |
| Intra-abdominal sepsis | Gram-negative bacilli including:  
  • Escherichia coli  
  • Pseudomonas aeruginosa | 60  
  40  
  30 | Ertapenem (if no risk of P. aeruginosa)  
  Piperacillin-tazobactam |
| Intra-abdominal sepsis | Gram-positive cocci including:  
  • Enterococcus sp.  
  • Anaerobes including  
  • Bacteroides sp.  
  • Fungi | 30  
  30  
  20  
  20 | Third- or fourth-generation cephalosporin (active against P. aeruginosa)  
  ± metronidazole  
  Imipenem or doripenem (high-risk patients)  
  ± fluconazole  
  ± aminoglycoside (if shocked) |
<table>
<thead>
<tr>
<th>Nosocomial Pneumonia</th>
<th>30–40</th>
<th>β-lactam (active against <em>P. aeruginosa</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>17-30</td>
<td>± aminoglycoside</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>7-15</td>
<td>± glycopeptide or linezolid if MRSA is suspected</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>3-5</td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>4-6</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pneumonia without risk factors for MRP</th>
<th>45</th>
<th>Third-generation cephalosporin without activity against <em>P. aeruginosa</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>45</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Alternative Gram-negative bacilli</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin Infections</th>
<th>40</th>
<th>β-lactam + β-lactamase inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus sp.</em></td>
<td>40</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus sp.</em></td>
<td>30</td>
<td>Piperacillin/tazobactam</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>10-20</td>
<td>Second-generation cephalosporins (such as cefoxitin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbapenems</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Catheter-related bloodstream infection</th>
<th>50</th>
<th>Glycopeptide or linezolid + β-lactam with activity against <em>P. aeruginosa</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus sp.</em></td>
<td>50</td>
<td></td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>30</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>10-15</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nosocomial meningitis</th>
<th>60</th>
<th>Meropenem + glycopeptide or linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-negative bacilli including <em>Acinetobacter sp.</em></td>
<td>60</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus sp.</em></td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus sp.</em></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
**Host characteristics**

For many years, the choice of antibiotics in the intensive care unit depended on the duration of prior hospitalization. The emergence of multi-resistant bacteria in the community has made this concept obsolete and there is, at present, a population of patients who carry multi-resistant bacteria. Risk factors for multi-resistant bacteria are: the prescription of an antibiotic treatment within the previous 3 months; a length of stay (hospital or ICU) > 5 days (this period is reduced if there is a high prevalence of multi-resistant bacteria locally); and, immunosuppression. In the presence of such risk factors, the spectrum of initial antibiotic treatment should include multi-resistant bacteria.

Routine tracheal aspiration makes it possible to prescribe adequate antibiotic therapy in 95% of the patients in whom ventilator-associated pneumonia is ultimately diagnosed by culture. This often involves an antibiotic active against MRSA, given with an antibiotic active against Gram-negative bacteria producing extended spectrum β-lactamase. For pneumonia, specific risk factors are: prior hospitalization for two days or more; residence in a nursing home or extended care facility; home infusion therapy or home wound care; chronic dialysis within 30 days; and, a family member with multi-resistant bacteria. These factors are listed in Figure 2.

**Figure 2**

[Diagram showing an algorithm for treating patients with life-threatening infection in intensive care unit. MRSA: methicillin-resistant Staphylococcus aureus; MRP: multi-resistant pathogen; *if renal failure]

### Site of infection

The site of infection is one of the major determinants in the choice of antibiotics (Table 1). Respiratory tract (63%), abdomen (20%), bloodstream infections (15%), and urinary tract infections (14%) are the most frequent types of intensive care unit infection reported. For patients without risk factors for multiresistant bacteria, in other words recent admission, no prior medical history, and no recent antibiotic use, ventilator-associated pneumonia is generally due to Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Legionella sp., Mycoplasma pneumoniae, Chlamydia pneumonia, and viruses. For the patients with risk factors for multi-resistant bacteria carriage, Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumonia, and MRSA should be suspected.
Sixty percent of spontaneous bacterial peritonitis episodes are produced by Gram-negative enteric bacilli - E. coli and Klebsiella sp. being the most frequent isolated micro-organisms. In ~ 25% of cases, streptococci (frequently pneumococcus) and enterococci are involved. Secondary peritonitis is always polymicrobial with Gram-negative bacteria (E. coli, Enterobacter sp., Klebsiella sp.), Gram-positive bacteria (enterococci in ~ 20% of the cases), and anaerobes (Bacteroides sp. in ~ 80% of the cases). For patients with identified risk factors, as defined in Figure 2 or those with nosocomial peritonitis, multi-resistant bacteria (including P. aeruginosa, Acinetobacter and MRSA) and yeasts should be suspected. In certain centres, either ‘expanded’ or ‘extended’-spectrum β-lactamase-carrying bacteria should be suspected and the empirical antibiotic treatment modified accordingly.

Skin infections are frequently polymicrobial. Suspected bacteria should be Streptococcus sp. (40%), S.aureus (30%), anaerobes (30%), and Gram-negative bacteria (10-20%). Bacterial cerebrospinal fluid infections in patients admitted from the community are due to S. pneumoniae (35%) and Neisseria meningitidis (32%). In the intensive care unit, they are related to intracerebral devices. Among 84 patients with ventriculostomy catheters, infections were related to Gram-negative bacilli (Acinetobacter sp. (50%) and Gram-positive cocci (29%).

Knowledge of local ecology

Knowledge of local bacteriological patterns increases the likelihood of prescribing appropriate antimicrobial therapy. Regular surveillance cultures are recommended to assess the level of resistance in a specific unit. This process is useful to identify patients carrying multi-resistant bacteria. Regular surveillance of cultures is also important to guide revisions of protocols in the light of local ecology changes. However, previously published results are not supportive; this might be due to a low prevalence of surveillance, and more recent data have shown a benefit. The value of knowledge of the local ecology is illustrated in several studies. In an observational study, using a local ecology-based protocol, 36 patients with late-onset ventilator-associated pneumonia were treated with β-lactam antibiotics with activity against P. aeruginosa. According to American Thoracic Society guidelines, 55 patients in this study should have received antibiotics with activity against P. aeruginosa. However, reduced renal clearance increases the likelihood of toxicity and once-daily dosing is strongly encouraged. The first dose should be the same in all patients, whatever the degree of renal insufficiency. It is recommended the prescription is limited to three days maximum. In this situation no dose adaptation is needed. For the β-lactam antibiotics, the serum levels must be above the minimum inhibitory concentrations (MIC) of the pathogens for all of the time between two injections. For fluoroquinolone antibiotics a high ratio of area under the curve to MIC is recommended (> 125 or 250 depending on the drug) and β-lactam antibiotics or quinolones should be administered at high doses or by continuous infusion (for example, ceftazidime). Vancomycin can also be administered by continuous infusion. If there is renal impairment, however, a corresponding dose reduction is needed. It has been shown that the glomerular filtration rate, mechanical ventilation, and admission diagnosis may influence the achieved concentrations of ceftazidime. Prediction of the penetration of antibiotics into solid organs remains a real challenge in the ICU. Future studies using microdialysis will be useful to make progress in this field, and result in improved monitoring of antibiotic levels in the interstitial fluid.
Monotherapy versus combination therapy

Combinations of antibiotics are used to widen the spectrum of activity of antimicrobial therapy, to increase the bactericidal activity, and to prevent the development of resistance. Textbooks and guidelines advise combinations for specific pathogens, mainly P. aeruginosa. A suspicion of multi-resistant bacteria leads to the use of a combination of antibiotics to enhance the spectrum and in septic shock a combination of antibiotics is also recommended. Using a propensity-matched analysis, combination therapy was associated with decreased 28-day mortality in septic shock patients. The beneficial impact of combination therapy was seen when used for either Gram-positive or Gram-negative infections. However, it seems that the beneficial effect was restricted to patients treated with a β-lactam antibiotic as the pivotal antibiotic, in combination with aminoglycosides, fluoroquinolones, or macrolides/clindamycin. Combination therapy was also associated with significant reductions in ICU and hospital mortality. This finding has been confirmed by another observational study. Of note, in a recent meta-analysis of studies of septic shock patients, it was observed that the use of combination therapy may be detrimental in patients with a mortality risk < 15% compared with high-risk patients (risk of death > 15%) (Odds Ratio 1.53; 95% Confidence Interval 1.16-2.03, p = 0.003). There is a clear need for a randomized clinical trial.

Adjunctive measures before instituting antimicrobial therapy

Obtaining samples for microbiological investigation is obligatory before initiating empirical antimicrobial therapy. At least two sets of blood cultures should be obtained, with at least one set drawn percutaneously and one set drawn through each vascular device, unless the device was recently inserted (< 3 to 5 days). Positive blood cultures make it possible to identify with certainty the pathogen(s) responsible for infection. Cultures of urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids should be obtained as soon as possible, and before antimicrobial therapy is initiated, except in very specific situations such as meningococcal septicaemia with purpura fulminans. A sample of urine is required to detect antigens against Legionella pneumophila. Because antimicrobial therapy should be initiated within the first hour of the diagnosis of severe sepsis, appropriate cultures should be collected within the first minutes after sepsis is suspected. There is no reason why collecting samples should lead to delays in prescribing antibiotics.

In addition to antimicrobial therapy, it is essential control the source of infection and modify factors that promote microbial growth or impair host antimicrobial defences. This includes drainage of an abscess or local focus on infection, debridement of infected necrotic tissue, and the removal of potentially infected devices. Delays in source control of an intra-abdominal infection is associated with increased mortality.

De-escalation strategy

Empirical antimicrobial therapy in life-threatening situations should be initiated promptly and should have a broad spectrum of activity that covers all potential antimicrobial-resistant pathogens. However, to reduce excessive antimicrobial usage, broad-spectrum therapy should be de-escalated on the basis of microbiological data and clinical response. This strategy has been used successfully in patients with pneumonia. For example, in patients with ventilator-associated pneumonia, de-escalation was possible in ~ 50% of patients on day 3, including 54% of ventilator-associated pneumonia episodes due to P. aeruginosa, A. baumannii and MRSA. This strategy appears to limit the emergence of resistance when indirectly assessed by the profile of bacteria involved in recurrent infections. In observational studies, de-escalation therapy was shown to be safe in patients with septic shock or ventilator-associated pneumonia. In patients with infections related to multiply resistant bacteria, de-escalation is often not possible. In patients with negative microbiology cultures, de-escalation is feasible if the patient is clinically stable. However, good quality studies which demonstrate the safety of such a strategy in unstable patients are lacking. In the absence of randomized clinical trials, it is not possible to exclude a negative effect. Nevertheless, because of its benefit and lack of demonstrable risks, de-escalation therapy should be used whenever possible in critically ill patients with severe infections.
Shortening the duration of antimicrobial therapy

Shortening the duration of antibiotic therapy makes it possible to curtail the development of multi-resistant bacteria, as well as the recurrence of infections caused by antimicrobial-resistant pathogens. In a randomized trial, the clinical pulmonary infection score was used as the criterion for decision-making regarding antibiotic therapy. Patients with clinical pulmonary infection score ≤ 6 were randomized to receive either standard therapy or ciprofloxacin monotherapy, with re-evaluation at day 3 and discontinuation of the ciprofloxacin if the score remained ≤ 6 at day 3. Antibiotics were continued beyond day 3 in 90% of the patients in the standard therapy group compared with 28% in the experimental therapy group. Antimicrobial resistance, or super-infections or both, developed in 15% of the patients in the experimental arm versus 35% of the patients in the standard therapy group. In a prospective follow-up of patients with suspected ventilator-associated pneumonia and culture-negative broncho-alveolar lavage, discontinuation of antibiotics before day 3 appeared to be safe. In conclusion, discontinuation of antibiotics, if appropriate cultures remain negative at day 3, appears safe in the patients making good clinical progress.

In patients with documented infection, a shortened duration of antimicrobial therapy minimizes the emergence of resistance. A randomized clinical trial was designed to determine whether 8 days of antibiotic treatment is as effective as 15 days in patients with microbiologically proven ventilator-associated pneumonia. Among patients who received appropriate initial empirical therapy, with the possible exception of those developing non-fermenting Gram-negative bacillus infections, comparable clinical effectiveness was seen with both the 8- and 15-day regimens. Among patients who developed recurrent infections, multi-resistant pathogens emerged less frequently in those who had received 8 days of antibiotics. Similarly, for patients with spontaneous bacterial peritonitis, there is no advantage in providing cefotaxime for more than 5 days. Although no randomized clinical trials are available in patients with intra-abdominal infection, observational data encourage the reduction in the duration of antibiotic therapy. Thus, discontinuing antibiotics if appropriate cultures are negative on day 3, as well as reducing the duration of antimicrobial therapy in proven infections, are efficient ways to curtail the development of antimicrobial-resistance. Recommended durations of treatment according to the site of infection are provided in Table 2.

Table 2
Duration of antibiotic therapy based on Infectious Diseases Society of America guidelines.

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Duration of antibiotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung infection:</strong></td>
<td></td>
</tr>
<tr>
<td>Community-acquired pneumonia due to S. pneumoniae</td>
<td>8 days</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>8 days*</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia and immunosuppression</td>
<td>14 days</td>
</tr>
<tr>
<td>Pneumonia due to L. pneumophila</td>
<td>21 days</td>
</tr>
<tr>
<td>Pneumonia with lung necrosis</td>
<td>≥ 28 days</td>
</tr>
<tr>
<td><strong>Intra-abdominal infections:</strong></td>
<td></td>
</tr>
<tr>
<td>Community peritonitis</td>
<td>&lt; 8 days</td>
</tr>
<tr>
<td>Postoperative peritonitis</td>
<td>14 days</td>
</tr>
<tr>
<td><strong>Central nervous system infections:</strong></td>
<td></td>
</tr>
<tr>
<td>Meningococemia</td>
<td>5 to 8 days</td>
</tr>
<tr>
<td>Meningitis due to S. pneumoniae</td>
<td>10-14 days</td>
</tr>
<tr>
<td>Postoperative meningitis due to S. epidermidis or enterobacteriacae</td>
<td>14 days</td>
</tr>
<tr>
<td>Meningitis due to L. monocytogenes</td>
<td>21 days</td>
</tr>
<tr>
<td>Postoperative meningitis due to S. aureus or P. aeruginosa</td>
<td>21 days</td>
</tr>
<tr>
<td>Site of infection</td>
<td>Duration of antibiotic therapy</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Brain abscess</td>
<td>≥ 28 days</td>
</tr>
<tr>
<td>Catheter-related bacteraemia:</td>
<td></td>
</tr>
<tr>
<td>S. epidermidis or enterobacteriacae</td>
<td>&lt; 8 days</td>
</tr>
<tr>
<td>S. aureus / Candida sp. (uncomplicated)</td>
<td>14 days</td>
</tr>
<tr>
<td>S. aureus (complicated)</td>
<td>≥ 28 days</td>
</tr>
</tbody>
</table>

*Pseudomonas aeruginosa may need 14 days or more*

Biomarkers may be useful in shortening the duration of antimicrobial therapy. Procalcitonin is a surrogate marker for estimating the likelihood of a bacterial infection. Procalcitonin-guided termination of antibiotic therapy may be a novel approach to reduce antibiotic overuse. Procalcitonin measurements, integrated into clinical algorithms, have been shown to reduce the duration of antibiotic courses by 25-65% in both hospitalized and more severely ill patients with community-acquired pneumonia and sepsis.⁵⁴ In contrast, to date, there is no evidence to use procalcitonin as a diagnosis marker for initiating an antimicrobial treatment.

Writing a formal protocol based on local ecology

Antimicrobial guidelines are useful tools to control antibiotic prescription, which in turn reduce the development of multi-resistant bacteria. Inappropriate treatment of infections is often due to either a lack of a suitable protocol, or violation of the protocol where one exists.⁵⁵ In one observational study, antibiotic choices were determined by staff including ICU and microbiologists. The choices were described in edited protocols, which were available in an electronic format on the ICU intranet. Interestingly, the four patients whose death was related to ventilator-associated pneumonia received treatments in violation of the guidelines.⁹ When the selection of antibiotics is left solely to the discretion of the attending physician, the rate of appropriate use is very low (49%).⁵⁶ A formalized antibiotic discontinuation policy reduced the duration of antibiotics, and may reduce the antibiotic resistance profile.⁵⁷

Conclusion

An integrated strategy to assist management of antimicrobial treatment for septic patients should be formalized with written protocols. The strategy includes rational use of empirical antimicrobial therapy considering local patterns of susceptibility of pathogens, prior history of patients, and their clinical status, followed by an early re-assessment to focus on the bacteria responsible for the infection. An infectious disease specialist may improve the accuracy of the prescription of the antimicrobial treatment in the ICU. In other areas, antimicrobial therapy can be administered according to practice guidelines that are designed in collaboration with the microbiology department. Antimicrobial treatment may be evaluated during a weekly staff meeting. Implementing such strategies reduces the duration of antibiotic treatment, length of stay, and improves local adherence to the guidelines. De-escalation should be performed systematically whenever it is possible, but escalation can also be considered when an early clinical response is not obtained or initial treatment is inappropriate. After microbiological documentation, prolonged antimicrobial therapy should remain the exception to the rule. In most situations seven days of treatment is a desirable goal. All efforts should be made to avoid excessive antimicrobial use for non life-threatening infections. However, there is a need for randomized clinical trials to provide support for this approach.
Key learning points

- Antibiotic therapy is the most powerful weapon for the treatment of septic shock
- Antibiotics should be administered within 60 minutes of the diagnosis of septic shock
- An antibiotic combination should be always used: a beta-lactam antibiotic as the pivotal antibiotic together with an aminoglycoside or a fluoroquinolone
- As many samples as needed should be collected to ensure a correct diagnosis of the source of infection
- After results of cultured samples are obtained treatment should be re-evaluated to either de-escalate or escalate the antibiotic treatment
- Written protocols should be available to guide the choice of antibiotic treatment according to the suspected source of infection.

Compliance to these protocols should be regularly monitored.

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