Overview of antimicrobial therapy in intensive care units


Julien Textoris¹, Sandrine Wiramus¹, Claude Martin¹ and Marc Leone²

¹Service d'Anesthésie et de Réanimation, Hôpital Nord, Assistance Publique-Hôpitaux de Marseille, Université de la Méditerranée, Marseille, France
²Département d’Anesthésie et de Réanimation, CHU Nord, Chemin des Bourrely, 13915 Marseille cedex 20, France

Author for correspondence:
Tel.: +33 491 968 650
Fax: +33 491 962 818
marc.leone@ap-hm.fr

In the management of a patient with severe sepsis, it is important to suspect the infection early, to collect samples immediately after diagnosis and to promptly initiate a broad-spectrum antibiotic treatment. The choice of this empirical antimicrobial therapy should be based on host characteristics, site of infection, local ecology and pharmacokinetics/pharmacodynamics of antibiotics. In severe infection, guidelines recommend the use of a combination of antibiotics. After results of cultures are obtained, treatment should be re-evaluated to either de-escalate or escalate the antibiotic prescription. This is associated with optimal costs, decreased incidence of superinfection and minimal development of antimicrobial resistance. All these steps should rely on written protocols, and the compliance to these protocols should be continuously monitored in order to detect violations and implement corrective procedures.

**Keywords:** antibiotic • de-escalation • empiric • sepsis

More than 75% of critically ill patients receive at least one antibiotic during their stay in hospital. The rationale for administering antibiotics is that patients with a microbiologically confirmed infection have a greater mortality rate compared with patients without infection [1]. Prompt initiation of appropriate antimicrobial therapy, which is defined by the effectiveness of treatment against the microorganisms responsible for the infection, saves lives and money in severely ill patients [2]. However, the emergence of multidrug-resistant bacteria is related to excessive antimicrobial use [3]. Thus, strategies such as de-escalation, which maximizes the likelihood of providing appropriate antimicrobial therapy and minimizes the risk of development of bacterial resistance, need to be encouraged [4–6]. We will describe thereafter these strategies. This article is based on the analysis of PubMed using 'sepsis', 'empirical', and 'antibiotic' or 'antimicrobial' as keywords. The search focused on the 2005–2010 period but previous references were added at the author convenience. References related to critically ill patients were selected. Whenever possible, the guidelines from professional societies were cited.

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 microorganism causing an infection is known. 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 [7]. Thus, inappropriate empirical antimicrobial therapy is defined as follows: the absence of antimicrobial agents directed against a specific class of microorganisms and administration of an antimicrobial agent to which the microorganism responsible for infection is resistant [8].

'Broad-spectrum antibiotics' refers to antibiotics with activity against *Pseudomonas aeruginosa* including imipenem–cilastatin, piperacillin–tazobactam, ceftazidime or ciprofloxacin while 'broad-spectrum antimicrobial therapy' refers to the combination of antibiotics with activities against *P. aeruginosa* and oxacillin-resistant *Staphylococcus aureus* (ORSA). In particular, addition of aminoglycosides to β-lactam is considered a broad-spectrum therapy. Limited-spectrum antibiotics will only refer to β-lactam without activity against *P. aeruginosa* (i.e., ceftiraxone and amoxicillin–clavulanate) [8].

**Rationale for administering an empirical antimicrobial therapy**

**Principles**

Empirical antimicrobial therapy should be used when a suspected infection can impair the 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 [8–11]. Patients suspected of having an
infection and hemodynamic impairment, that is, requiring a fluid challenge or vasopressors, are candidates for receiving an empiric antimicrobial therapy. Antimicrobial therapy is also required in selected infections, such as severe sepsis, meningitis, pneumonia, peritonitis, pyelonephritis or endocarditis, or in specific patient populations (Figure 1). The timing of antibiotic administration is critical, impacting the outcome (Figure 1). In patients with severe infection, any delay is associated with increased mortality and morbidity [12]. One cannot recommend waiting for results of microbiological culture before introducing antibiotics in specific groups of patients.

The selection of initial antibiotic therapy is based on risk factors for specific pathogens, modified by knowledge of local patterns of antibiotic resistance and organism prevalence [13]. This treatment should be efficient against the bacteria involved in the suspected infection. Indeed, inappropriate empiric antibiotic therapy is widespread and associated with increased mortality in critically ill patients. For instance, increased mortality in patients was related to empirical piperacillin–tazobactam therapy and *P. aeruginosa* bacteremia owing to isolates with reduced piperacillin–tazobactam susceptibility [14]. The challenge is to provide an appropriate therapy without any microbiological documentation. In this setting, the adherence to guidelines seems to be associated with an increased rate of appropriation [15]. 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 intensive care unit (ICU) stay [16]. Barriers to physician guidelines adherence include awareness, familiarity, agreement, self-efficacy, outcome expectancy, ability to overcome the inertia of previous practice and absence of external barriers to perform recommendations [17].

In order to minimize the risk of failure, the empirical antimicrobial therapy is typically broad spectrum. However, the major limitation to this clinical approach is that it consistently leads to more antibiotic therapy than when the decision is based on the findings of cultures [18]. This practice can be associated with the emergence of multidrug-resistant pathogens (MRPs), infections due to *Clostridium difficile* and increased costs [8]. In parallel, as the evidence for administering an empirical antibiotic is not always found [19,20], it is important to determine the conditions requiring emergent administration of antibiotics. In all patients, any empiric antibiotic regimen should be reassessed and tailored as soon as culture and sensitivity results become available. This practice, which usually implies de-escalation (but sometimes escalation if pathogens are not covered), is associated with optimal costs, decreased incidence of superinfection and minimal development of antimicrobial resistance [8]. *Candida* colonization and invasive candidasis in an ICU is a major nosocomial problem. There is an obvious relationship between the use of antibacterial agents and subsequent *Candida* colonization. Consequences of antibiotic overuse are well described and beyond the scope of this article [21,22].

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

In each patient, the timing for starting an antibiotic can be considered as emergent, urgent and delayed (Figure 1). Emergent and urgent are defined by the need for starting antibiotics within 1 h and 6–8 h after diagnosis has been performed, respectively. Delayed antibiotic therapy is defined by the start of antibiotics from 8–24 h after diagnosis [23].

Emergent indications of empirical antimicrobial therapy concern many ICU patients. It should be used in patients with hemodynamic impairment and suspected infection. Severe sepsis is defined by the association of signs of sepsis and organ dysfunction (i.e., cardiovascular, pulmonary, neurologic and hepatic). Septic shock is defined by the need to introduce vasopressors in a patient with a suspected infection [24]. 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 [2]. Each hour of delay in antibiotic administration after diagnosis has been associated with an average decrease in survival of 7.6%; every 10 min, survival is decreased by 1%. Thus, guidelines recommend prompt antimicrobial therapy in these patients [25]. Several observational studies confirmed a strong association between prompt introduction of antibiotics and survival [26–28]. They underline the need to provide efficient antibiotics within the first hour after sepsis identification. Indeed, the empirical antibiotic therapy should be immediately appropriate [8]. Inappropriate initial antimicrobial therapy for septic shock occurs in approximately 20% of patients and is associated with a fivefold reduction in survival [29]. Bacterial meningitis is another indication

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**Figure 1. Indications and best timing for starting antibiotic therapy.** Best timing for providing an empirical antimicrobial treatment: emergent (top), urgent (middle) and delayed (bottom). Light gray portions represent the maximal time requested before antibiotic administration.

VAP: Ventilator-associated pneumonia.
of emergent antimicrobial therapy. In an observational study, an interval between admission and antibiotic therapy above 3 h was the strongest indicator of mortality, with an odds ratio of 14 [30]. Sepsis in splenectomized or neutropenic patients should be treated without delay. After splenectomy, pneumococcal infection accounts for 50–90% of cases and may be associated with mortality of up to 60% [31]. Importantly, despite the emergent need for treatment, if possible, samples should be collected before the first administration of antibiotics [25]. In a large observational study, obtaining blood cultures before antibiotics were administered was associated with improved survival [26]. Although this result perhaps only reflects good practices, obtaining blood culture may also serve to refine the treatment after bacteriological results are obtained.

Urgent antibiotic therapy is probably the most common situation encountered in patients with infection. In these patients, samples are collected before starting antibiotics. Gram stain results may help in the choice of antibiotics [32]. However, the actual contribution of Gram stain in the choice of empirical treatment remains a conflicting issue. Progressive change in the clinical picture over hours can favor the starting of antibiotic therapy. This is frequent in mechanically ventilated patients with fever, in whom the images on chest x-ray worsen over the course of a day. Sometimes, other investigations, such as CT scan or ultrasound may serve to confirm the diagnosis. Indeed, CT scan improves the accuracy of diagnosing and typing of pneumonia [33]. Ultrasound provides a diagnostic modality that allows a whole-body approach at the bedside of a critically ill patient in the search for infectious foci [34]. This procedure requires an educational program but may avoid unnecessary transport of patients. In clinical practice, antibiotics should be used in these patients immediately if infection is obvious or if the patient is unstable.

With respect to community-acquired pneumonia, the first antibiotic dose should be administered while still in the emergency department [35]. In elderly patients with community-acquired pneumonia, adherence to American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines was associated with a decreased time to achieve clinical stability compared with nonadherence. Implementation of national guidelines at the local hospital level will improve not only mortality and length of stay of elderly patients hospitalized with community-acquired pneumonia but also time to clinical stability [36,37]. Adherence to guidelines depends on the hospital, the specialty and training status of prescribing physicians. Nonadherence is higher in non-pneumology specialists [38].

With regard to hospital-acquired pneumonia, ATS guidelines underline that 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) represent the most accurate combination of criteria for starting empiric antibiotic therapy [13,39]. Prompt empiric therapy should be considered for all patients suspected of having hospital-acquired pneumonia. Elsewhere, guidelines recommend that antimicrobial therapy be started immediately, particularly if the patient is unstable [40]. Adherence to guidelines can improve the rate of appropriation and the clinical response, but it does not influence mortality [15,41]. In clinical practice, these guidelines seem to have an excellent negative predictive value and a low positive predictive value in predicting infection or colonization with MRP at ICU admission [42].

With respect to intra-abdominal infection, it is clearly stated that antimicrobial therapy should be initiated promptly, usually in the emergency department. A common error is to administer antibiotics after the source control in order to collect samples before antimicrobials are administered. Antimicrobial therapy should be initiated once a patient receives a diagnosis of an intra-abdominal infection or once such an infection is considered likely. For patients with septic shock, antibiotics should be administered as soon as possible and no later than 1 h after the diagnosis. In other patients, antibiotics are started in the emergency department. Satisfactory antimicrobial drug levels should be maintained during the source control intervention, which may necessitate additional administration of antibiotics just before the onset of the procedure [43].

With respect to catheter-associated urinary tract infection, guidelines do not indicate the best timing for initiating antibiotics. However, a specimen of urine should be obtained prior to initiating the treatment [44]. The patients clinical status should lead to the treatment decision. In patients without fever, there is no indication for administering any antibiotics [45].

Choice of empirical antimicrobial therapy

A judicious choice of antimicrobial therapy should be based on the host characteristics, site of infection, local ecology, and the pharmacokinetics/pharmacodynamics of antibiotics. Toxicity and costs should also be considered. The best option between monotherapy and combination of antibiotics will be discussed later. Antimicrobial options for severe nosocomial infections are suggested in Table 1. As guidelines have specifically described the use of antibiotics in each condition, hereafter we only report the principles of antibiotic choice.

Host characteristics

For many years, the choice of antibiotics in the ICU depended on the duration of prior hospitalization. The emergence of MRP in outpatients has made this concept obsolete. Hence, there is at present a population of outpatients at risk of carriage of MRP [13,46]. Risk factors for MRP are: the prescription of an antibiotic treatment within 3 months; a length of stay (hospital or ICU) over 5 days (this delay should be reduced if there is a local high prevalence of MRP); or immunosuppression [13]. Therefore, in the presence of such risk factors, the spectrum of initial antibiotic treatment should include MRP. Routine endotracheal aspiration makes it possible to prescribe adequate antibiotic therapy in 95% of the patients in whom ventilator-associated pneumonia is ultimately diagnosed by culture [32]. This often involves an antibiotic active against ORSA, associated with an antibiotic active against Gram-negative bacteria producing extended-spectrum β-lactamase. For pneumonia, specific risk factors are: prior hospitalization for 2 days or more; residence in a nursing home or extended care facility; home
infusion therapy or home wound care; chronic dialysis within 30 days; or knowledge of a family member with MRP. These risk factors are described in Figure 2.

Importance of site

The site of infection is one of the major determinants in the choice of antibiotics (Table 1). Respiratory tract (63%), abdomen (20%), bloodstream (15%) and urinary tract infections (14%) are the most frequent types of ICU infection reported [46]. For patients without risk factors for MRP, that is, recent admission, no prior medical history and no recent antibiotic use, ventilator-associated pneumonias is generally related to Streptococcus pneumoniae, Haemophilus influenzae, S. aureus, Legionella sp., Mycoplasma pneumoniae, Chlamydia pneumonia and viruses [102–107]. For patients with risk factors of MRP carriage, P. aeruginosa, Acinetobacter baumannii, Klebsiella pneumonia and ORSA should be suspected [13,40].

A total of 60% of the spontaneous bacterial peritonitis episodes are produced by Gram-negative enteric bacilli – Escherichia coli and Klebsiella sp. being the most frequently isolated microorganisms. In approximately 25% of the cases, streptococci (frequently pneumococcus) and enterococci are involved [47]. Secondary peritonitis are polymicrobial with Gram-negative bacteria (Enterobacteriaceae, P. aeruginosa) and Gram-positive bacteria (S. aureus, S. pneumoniae) and yeasts should be suspected [43]. In certain centers, 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 Staphylococcus sp., Streptococcus sp., and Gram-negative bacilli [13,40]. For patients with identified risk factors, or those with tertiary peritonitis, multiresistant bacteria (including P. aeruginosa, Acinetobacter and ORSA) and yeasts should be suspected [43]. In certain centers, extended-spectrum β-lactamase-carrying bacteria should be suspected and the empirical antibiotic treatment modified accordingly.

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Table 1. Bacteria potentially responsible for sepsis depending on the site of infection.

<table>
<thead>
<tr>
<th>Site</th>
<th>Bacteria</th>
<th>Suggested treatment†</th>
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</thead>
<tbody>
<tr>
<td>Urinary tract infections</td>
<td>Escherichia coli</td>
<td>Ceftriaxone iv. or ceftazidime (if suspicion of P. aeruginosa) ± Aminoglycoside</td>
</tr>
<tr>
<td>Severe acute pyelonephritis</td>
<td>Pseudomonas aeruginosa, Enterococcus sp., Staphylococcus sp.</td>
<td></td>
</tr>
<tr>
<td>Intra-abdominal sepsis</td>
<td>E. coli, P. aeruginosa, Enterococcus sp., Bacteroides sp., Fungi.</td>
<td>Ertapenem (no risk for P. aeruginosa) Piperacillin–tazobactam Third- or fourth-generation cephalosporin (active against P. aeruginosa) + metronidazole Imipenem or doripenem (high-risk patients) ± Fluconazole ± Aminoglycoside (shock)</td>
</tr>
<tr>
<td>Nosocomial pneumonia</td>
<td>Enterobacteriaceae, P. aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae.</td>
<td>β-lactam (active against P. aeruginosa) ± Aminoglycoside ± Glycopeptide or linezolid if ORSA is suspected</td>
</tr>
<tr>
<td>Pneumonia without risk factors for MRP</td>
<td>S. aureus, S. pneumoniae, H. influenzae, Alternative Gram-negative bacilli, Anaerobes</td>
<td>Third-generation cephalosporin without activity against P. aeruginosa ± Macrolide (if intracellular bacteria are suspected)</td>
</tr>
<tr>
<td>Skin infections</td>
<td>Streptococcus sp., Staphylococcus sp., Anaerobes, Gram-negative bacilli</td>
<td>β-lactam + β-lactamase inhibitor Piperacillin–tazobactam Second-generation cephalosporins (such as cefoxitin) Carbapenems</td>
</tr>
<tr>
<td>Catheter-related bloodstream infection</td>
<td>Staphylococcus sp., Enterobacteriaceae, P. aeruginosa</td>
<td>Glycopeptide or linezolid + β-lactam with activity against P. aeruginosa</td>
</tr>
<tr>
<td>Nosocomial meningitis</td>
<td>Acinetobacter sp., Staphylococcus sp., Streptococcus sp., Neisseria meningitidis</td>
<td>Meropenem + glycopeptide or linezolid</td>
</tr>
</tbody>
</table>

†Antibiotic options in severe infections.

d.: Intravenous; MRP: Multidrug-resistant pathogen; ORSA: Oxacillin-resistant Staphylococcus aureus.

Bacterial etiologies were summarized from [102–107].
ventriculostomy catheters, infections were related to Gram-negative bacilli (50% *Acinetobacter sp.*) and Gram-positive cocci (29%) [49].

**Knowledge of local ecology**

Knowledge of local bacteriologic patterns increases the likelihood of prescribing appropriate antimicrobial therapy. The value of regular surveillance cultures for guiding the empirical therapy is suggested for assessing the level of resistance in a specific unit. This process is useful to identify the patients carrying MRP. The regular surveillance of cultures is critical to revise the protocol according to local ecology changes. On this topic, published results are rather negative, but this might be because of a low prevalence of surveillance [50,51]. Indeed, more recent data show a benefit of using these regular cultures to guide empirical treatments [52–54]. The value of local ecology knowledge has been illustrated in several studies [8,55]. In an observational study, using a local ecology-based protocol, 36 patients with late-onset ventilator-associated pneumonia were treated with β-lactams with activity against *P. aeruginosa* [8]. According to ATS guidelines, 55 patients in this study would require such antibiotics [13]. Thus, knowledge of local ecology made it possible to use narrower-spectrum antibiotics in 19 patients, as compared with the ATS guidelines. However, if knowledge of local epidemiology data is important for ICU-acquired infection, this is not true for community or healthcare-acquired infections.

**Pharmacokinetics/pharmacodynamics of antibiotics**

The pharmacokinetics of antibiotics is modified in ICU patients owing to the large daily fluid balance, acute changes in bodyweight, hypoalbuminemia, edema and low hematocrit values, which leads to a marked change in elimination half-life, volume of distribution and clearance. On the other hand, sepsis increases capillary permeability, with the formation of a ‘third-spacing’, resulting in higher antibacterial clearances. Alternatively, multiple organ dysfunction causes a decrease in antibacterial clearance. Consequently, therapeutic drug monitoring of plasma concentrations should be encouraged whenever possible, because these concentrations are difficult to predict in critically ill patients, even when their renal function is estimated using different formulae [56].

The pharmacokinetics of concentration-dependent antibiotics such as aminoglycosides are affected by an increased volume of distribution in sepsis, resulting in decreased peak serum concentrations, but reduced renal clearance would increase the likelihood of toxicity. The use of once-a-day dosing is strongly encouraged.

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**Table 2. Pharmacokinetics criteria to determine an adequate dosing of antibiotics.**

<table>
<thead>
<tr>
<th>Properties</th>
<th>Objective</th>
<th>Dosing</th>
<th>Antibiotics</th>
</tr>
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<tbody>
<tr>
<td>Time-dependent effects</td>
<td>Maximal time above MIC or maximal AUC/MIC</td>
<td>Repeated high dosing or continuous infusion</td>
<td>β-lactams, quinolones, vancomycin</td>
</tr>
<tr>
<td>Concentration-dependent effects</td>
<td>Maximum peak level</td>
<td>High once-daily dosing</td>
<td>Aminoglycosides</td>
</tr>
</tbody>
</table>
The first dose should be the same in all patients, whatever the degree of renal insufficiency. It is strongly recommended to limit prescriptions to 3 days maximum. Thus, no dose adaptation is needed in any patients (Table 2) [57,58]. For the β-lactams, the serum levels must be above the MICs of the pathogens for 100% of the time between two injections [59]. For quinolone, a high ratio of AUC/MIC is required (>125 or 250 depending on the drugs). For this purpose, β-lactams or quinolones should be administered at higher doses or by continuous infusion (e.g., ceftazidime); vancomycin can also be administered by continuous infusion [60,61]. However, if there is renal impairment, a corresponding dose reduction is needed. It has been shown, for instance, that the glomerular filtration rate, mechanical ventilation and admission diagnosis may influence the achieved concentrations of ceftazidime [62]. The model allows the a priori dosing to be adjusted to the individual patient. Prediction of the penetration of antibiotics into solid organs remains a real clinical challenge in the ICU [63]. Future studies using microdialysis will be useful to make progress in this field, making it easy to monitor antibiotic levels in the interstitial fluid.

**Monotherapy versus combination therapy**

Combination of antibiotics is aimed at widening the spectrum of activity of antimicrobial therapy, increasing bactericidal activity and preventing the development of resistance. Textbooks and guidelines advise the combination of antibiotics for specific pathogens, mainly *P. aeruginosa* [64]. The suspicion of MRP leads to the administration of a combination of antibiotics for enhancing the spectrum. In septic shock, guidelines recommend the use of a combination of antibiotics. Using a propensity matched analysis, combination therapy was associated with decreased 28-day mortality of septic shock patients. The beneficial impact of combination therapy was found to apply to both Gram-positive and Gram-negative infections. However, it seems that the beneficial effect was restricted to patients treated with β-lactams as a pivotal antibiotic, in combination with aminoglycosides, fluoroquinolones or macrolides/clindamycin [65]. Combination therapy was also associated with significant reductions in ICU and hospital mortality. This finding is confirmed by another observational study [66]. Of note, in a recent meta-analysis, even if a decrease in mortality was associated with the use of combination therapy in septic shock patients, this strategy may be detrimental in patients with mortality risk below 15% [67]. This underlines the need for a randomized clinical trial.

Community-acquired pneumonia can be caused by intracellular bacterial infections, especially *Legionella pneumophila*. Thus, guidelines recommend the empirical use of macrolides or fluoroquinolones until urinary antigen detection results are obtained [68]. In this setting, a recent observational study shows a benefit to the use of a macrolide. Nevertheless, a meta-analysis shows that combination therapy is not needed for community-acquired pneumonia [69].

With respect to ventilator-associated pneumonia, a randomized clinical trial reported no difference in 28-day mortality between the combination and monotherapy groups. Duration of ICU and hospital stay, clinical and microbiological treatment response, emergence of antibiotic-resistant bacteria, isolation of *C. difficile* in stool and fungal colonization were also similar in the two groups. In a subgroup of patients who had infection due to *Pseudomonas* sp., *Acinetobacter* sp., and multidrug-resistant Gram-negative bacilli at enrollment (n = 56), the adequacy of initial antibiotics (84.2 vs 18.8%; p < .001) and microbiological eradication of infecting organisms (64.1 vs 29.4%; p = 0.05) were higher in the combination group compared with the monotherapy group [70]. In a study focusing on ventilator-associated pneumonia due to *P. aeruginosa*, initial use of combination therapy significantly reduces the likelihood of inappropriate therapy, which is associated with higher risk of death. However, administration of only one effective antimicrobial or combination therapy provides similar outcomes, suggesting that switching to monotherapy once the susceptibility is documented is feasible and safe [69].

For patients with severe generalized peritonitis, piperacillin–tazobactam (16 g/day) was compared with piperacillin–tazobactam (12 g/day) combined with amikacin (7.5 mg/kg twice daily). In fact, the addition of amikacin to piperacillin–tazobactam does not seem to be necessary [71]. As isolation of *Candida* species appears to be an independent risk factor of mortality in nosocomial peritonitis, the addition of drugs active against *Candida* to other antibiotics is suggested [72]. Overall, empirical antimicrobial therapy should target all the most probable pathogens potentially involved in the infective process. To achieve this objective, combination of antibiotics may be required.

Combination antimicrobial therapy is proposed for reducing the emergence of bacterial resistance. This has been clearly demonstrated for *Mycobacterium tuberculosis*. Antibiotics such as fusidic acid, fosfomycin, rifampicin or fluoroquinolones should not be used alone. However, there are no data supporting the beneficial effect of combination therapy for preventing emergence of resistance with usual antibiotics in the ICU. In a different setting, a meta-analysis showed absolutely no effect of antibiotic combination to prevent the emergence of resistance [73].

**Adjunctive measures before instituting antimicrobial therapy**

Once again, the microbiological documentation before initiating empirical antimicrobial therapy is an obligatory prerequisite. At least two blood cultures should be obtained with at least one drawn percutaneously and one drawn through each vascular device, unless the device was recently inserted. Positive blood cultures make it possible to identify with certainty the pathogen(s) responsible for infection. Of note, they should require management in ICU and are associated with a high mortality rate [74]. Cultures of urine, cerebrospinal fluid, wounds, respiratory secretions or other body fluids should be obtained as soon as possible, before antimicrobial therapy is initiated, except for very specific cases such as purpura fulminans. A urine sample is required to detect antigens directed against *L. pneumophila*. Because the antimicrobial therapy should be initiated within the first hour of recognition of severe sepsis [1], appropriate cultures should be
collected within the first minutes after sepsis is clinically suspected. If anything, collecting samples should never lead to delaying the prescription of antibiotics in case of severe infections.

In addition to antimicrobial therapy, it is mandatory in patients with severe sepsis or septic shock to control the source of infection and to modify factors that promote microbial growth or impair host antimicrobial defenses [75]. This consists of the drainage of an abscess or local focus on infection, the debridement of infected necrotic tissue and the removal of the potentially infected device. Delay in the source control of intra-abdominal infection is associated with increased mortality [44].

Prevention of emergence of bacterial resistance
Antibiotic use drives the emergence of resistance, which induces deleterious effects on the outcome of patients. This is clearly attested by two different studies. First, within a 6-year period, the increase in the number of strains of Gram-negative bacteria resistant to ciprofloxacin paralleled the increase in the use of fluoroquinolones [76]. Second, in a retrospective study, two major independent risk factors for mortality were identified: ORSA (OR: 5.90; 95% CI: 1.36–25.36) and P. aeruginosa (OR: 3.30; 95% CI: 1.04–10.4) [77]. Thus, prudent use of antibiotics may avoid over-mortality associated with infections due to difficult-to-treat bacteria.

However, the real impact of MRP on outcome is still a matter of debate. This is illustrated by the abundant literature on the impact of oxacillin resistance for S. aureus. Briefly, in a first study, after adjusting for confounding factors, S. aureus infection-related mortality remained significantly higher in patients with ORSA infection than in those with oxacillin-susceptible S. aureus infection, among those without pneumonia [78]. In a second study, after adjustment, oxacillin resistance did not affect ICU or hospital mortality rates [79]. In a third study, the patients with ventilator-associated pneumonia due to ORSA were significantly older than patients with oxacillin-susceptible S. aureus and more likely to be patients hospitalized in medical ICUs. Ventilator-associated pneumonia due to ORSA was associated with increased overall length of stay, compared with oxacillin-susceptible S. aureus-related ventilator-associated pneumonia. However, confounding factors can explain these differences [80]. In a fourth study, despite appropriate glycopeptide therapy, after adjustment for disease severity and diagnostic category, there was an increased attributable mortality for pneumonia by ORSA [81]. Thus, as nicely shown in a retrospective study, oxacillin resistance did not significantly affect 28-day mortality of patients with S. aureus ventilator-associated pneumonia receiving appropriate antibiotics [82]. The role of confounding factors remains unclear. Suggested strategies to reduce emergence of multidrug-resistant bacteria are listed in Box 1.

Reducing use of antimicrobial agents
In order to curtail the development of antimicrobial resistance, the first requirement is to use antimicrobial therapy only in the patient with documented infections, except if the infections are life-threatening [83]. Future studies are required in order to better differentiate infection and colonization [46]. As suggested elsewhere, in the future, strategies like ‘no antibiotics with watchful waiting and vigilant monitoring’ should perhaps be promoted for nonsevere infections [3].

De-escalation strategy
Empirical antimicrobial therapy in life-threatening situations should be initiated promptly and should have a broad-spectrum that covers all potential antimicrobial-resistant pathogens. To reduce excessive antimicrobial usage, broad-spectrum therapy should be de-escalated on the basis of microbiological data and clinical response [5,84,85]. This strategy has been successfully used in patients with pneumonia [6,9,10,86]. For patients with ventilator-associated pneumonia, de-escalation in a real-life study was possible in approximately 50% of patients on day 3, including 54% of ventilator-associated pneumonia episodes due to P. aeruginosa, A. baumannii and ORSA [9,15]. This strategy appears to limit the emergence of resistance, indirectly assessed by the profile of bacteria involved in recurrent infections. In observational studies, de-escalation therapy was also shown to be safe in patients with septic shock or ventilator-associated pneumonia. In patients with infections related to MRP bacteria, de-escalation is often not possible [87]. In patients with negative microbiology cultures, this strategy is feasible if clinical stability is obtained. However, good quality studies are lacking to demonstrate the safety of such a strategy in unstable patients. 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 duration of antimicrobial therapy
Reducing the duration of antibiotics makes it possible to curtail the development of multiresistant bacteria, as well as the recurrence of infections caused by antimicrobial-resistant pathogens. In a randomized clinical trial, clinical pulmonary infection score [88] was used as operational criteria for decision making regarding antibiotic therapy. Patients with a clinical pulmonary infection score less then 6 were randomized to receive either standard therapy or ciprofloxacin monotherapy with re-evaluation at day 3, with discontinuation of ciprofloxacin if clinical pulmonary infection score remained under 6 at day 3. Antibiotics were continued

Box 1. Suggested strategies to reduce bacterial resistance.

- Restrict antibiotic treatment for documented infections, except for life-threatening situations
- Avoid treating asymptomatic colonization
- Optimize pharmacokinetics/pharmacodynamics
- Use combination therapy in patients with shock
- Implement de-escalation strategies according to microbiological data and clinical evolution
- Shorten duration of antibiotic treatment whenever possible
- Identify a referent infectious disease specialist in the intensive care unit
- Review and discuss all antibiotic treatments periodically with all staff
beyond day 3 in 90% of the patients in the standard therapy group as compared with 28% in the experimental therapy group. Antimicrobial resistance or superinfections, or both, developed in 15% of the patients in the experimental arm versus 35% of the patients in the standard therapy group \[89\]. In a prospective follow-up of patients with suspected ventilator-associated pneumonia and culture-negative bronchoalveolar lavage, discontinuation of antibiotics before day 3 appears to be safe \[90\]. In conclusion, discontinuation of antibiotics if appropriate cultures remain negative at day 3 appears safe in patients with good clinical evolution.

In patients with documented infection, a reduced duration of antimicrobial therapy minimizes the emergence of resistance. A randomized clinical trial was aimed at determining whether 8 days is as effective as 15 days of antibiotic treatment of patients with microbiologically proven ventilator-associated pneumonia. Among patients who had received appropriate initial empirical therapy, with the possible exception of those developing non-fermenting Gram-negative bacillus infections, comparable clinical effectiveness against ventilator-associated pneumonia was obtained with the 8- and 15-day treatment regimens. Among patients who developed recurrent infections, multiresistant pathogens emerged less frequently in those who had received 8 days of antibiotics \[91\]. Similarly, for patients with spontaneous bacterial peritonitis, there is no advantage of administering cefotaxime for more than 5 days \[92\]. For patients with intra-abdominal infections, although no randomized clinical trials were available, observational data incite reducing the duration of antibiotics \[93\]. In conclusion, discontinuing antibiotics if appropriate cultures are negative after day 3 as well as reducing the duration of antimicrobial therapy in proven infection are efficient ways to curtail the development of antimicrobial resistance. Recommend duration of treatments according to the site of infection are given in Table 3.

Biomarkers may be useful in shortening the duration of antimicrobial therapy. Procalcitonin is a surrogate biomarker for estimating the likelihood of a bacterial infection. Procalcitonin-guided termination of antibiotic therapy may be a novel approach utilized to reduce antibiotic overuse. Procalcitonin measurements, integrated in clinical algorithms, have been shown to reduce the duration of antibiotic courses by 25–65% in hospitalized and more severely ill patients with community-acquired pneumonia and sepsis \[94–96\]. By contrast, to date, there is no evidence to use procalcitonin as a diagnostic marker for initiating an antimicrobial treatment.

### Elaborating formal protocol based on local ecology

Antimicrobial guidelines, automated antimicrobial utilization guidelines and edited protocols are useful tools for the control of antibiotic prescription, which in turn reduce the development of MRP \[15,97\]. Inappropriate treatment of infections is often secondary to the lack or violation of protocols \[15,98\]. In an observational study, the antibiotic choices were determined by staff including ICU and microbiologist physicians. These choices were consigned in edited protocols, which were available in an electronic form at the ICU intranet site \[8,15\]. Interestingly, the four patients whose deaths were related to ventilator-associated pneumonia received treatments in violation of our guidelines \[8,15\]. By contrast, when the selection of antibiotics is left to the discretion of the attending physician, the rate of appropriateness is very low (49%) \[99\]. A formalized antibiotic discontinuation policy reduced the duration of antibiotics, and thus may positively affect the antibiotic resistance profile \[100\]. Hence, policies aiming at controlling antibiotic prescription should be encouraged in order to reduce the development of antimicrobial resistance.

### Table 3. Predetermined duration of antibiotic therapy based on the Infectious Diseases Society of America guidelines.

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Duration of antibiotic therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung infection</strong></td>
<td></td>
</tr>
<tr>
<td>Community-acquired pneumonia due to Streptococcus pneumonia</td>
<td>8</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>8†</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia and immunodepression</td>
<td>14</td>
</tr>
<tr>
<td>Pneumonia due to Legionella pneumophila</td>
<td>21</td>
</tr>
<tr>
<td>Pneumonia with lung necrosis</td>
<td>≥28</td>
</tr>
<tr>
<td><strong>Intra-abdominal infections</strong></td>
<td></td>
</tr>
<tr>
<td>Community peritonitis</td>
<td>&lt;8</td>
</tr>
<tr>
<td>Postoperative peritonitis</td>
<td>14</td>
</tr>
<tr>
<td><strong>CNS infections</strong></td>
<td></td>
</tr>
<tr>
<td>Meningococcemia</td>
<td>5–8</td>
</tr>
<tr>
<td>Meningitis due to S. pneumoniae</td>
<td>10–14</td>
</tr>
<tr>
<td>Postoperative meningitis due to Staphylococcus epidermidis or Enterobacteriaceae</td>
<td>14</td>
</tr>
<tr>
<td>Meningitis due to Listeria monocytogenes</td>
<td>21</td>
</tr>
<tr>
<td>Postoperative meningitis due to Staphylococcus aureus or Pseudomonas aeruginosa</td>
<td>21</td>
</tr>
<tr>
<td>Brain abscess</td>
<td>≥28</td>
</tr>
<tr>
<td><strong>Catheter-related bacteremia</strong></td>
<td></td>
</tr>
<tr>
<td>S. epidermidis or Enterobacteriaceae</td>
<td>&lt;8</td>
</tr>
<tr>
<td>S. aureus/Candida sp. (uncomplicated)</td>
<td>14</td>
</tr>
<tr>
<td>S. aureus (complicated)</td>
<td>≥28</td>
</tr>
</tbody>
</table>

*Pseudomonas aeruginosa may need 14 days or more. Data from \[13,35,43,108–110\].

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\[90\] Textoris, Wiramus, Martin & Leone
Expert commentary & five-year view

Prescribing an empirical antimicrobial therapy is a major challenge for the intensivist. As reported elsewhere [101], the paradigm for treating sepsis, particularly nosocomial sepsis, is: ‘get it right the first time, hit hard upfront and use large doses of broad-spectrum antibiotics for a short period’. The management of a patient with severe sepsis is first to diagnose the infection early, to collect samples immediately after the diagnosis has been made, and to initiate a broad-spectrum combination of antibiotics based on the host characteristics, possible source of infection and local ecology. As soon as microbiological findings are available, this treatment should be de-escalated or stopped if the diagnosis of infection is ruled out. All these steps should rely on written protocols, and the compliance to these protocols should be continuously monitored in order to detect all violations.

The next challenge is to confirm the safety of this approach by high level clinical trials conducted in the ICU setting. The literature relies essentially on observational studies, which can be biased by several unknown factors or studies based on non-ICU patients. Thus, there is a need to test several hypotheses in well-conducted randomized clinical trials: combination therapy versus monotherapy and de-escalation versus conservative therapy. In this view, there is a need to improve the definition of patients requiring an empirical antimicrobial therapy. This concept is not discussed in patients with life-threatening infections. However, whether or not this concept should be applied to patients without life-threatening infections deserves supplementation, since the increase in selection pressure can offset the clinical benefit. Indeed, several studies do not confirm the benefit of the administration of empirical antibiotics in this setting [19,20].

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Key issues

- Early empirical antimicrobial therapy (within 60 min of the diagnosis) should be administered in patients with suspected severe infection.
- In this setting, empirical antimicrobial therapy usually consists of a combination of broad-spectrum antibiotics.
- Host characteristics, source of infection and local ecology are the determinants of choice of empirical antimicrobial therapy.
- De-escalation based on clinical response and microbiological findings is a prerequisite and may avoid the emergence of multidrug-resistant pathogens.
- Written guidelines are the best way to provide appropriate antibiotics in a timely fashion.
- Follow-up of the adherence to protocols is required in order to detect protocol violations.

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Overview of antimicrobial therapy in intensive care units

Review


