Appropriateness is Critical

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Despite considerable research and clinical effort, management of severe infections in critically ill patients remains an ongoing challenge for physicians. Increased severity of sickness and aggressive medical management, together with reduced susceptibilities of nosocomial pathogens, dramatically increase the complexity of managing severe infections in the intensive care unit (ICU). Critically ill patients are most significantly affected by this issue because it has been estimated than more than 70% are prescribed antibiotics during their ICU stay.\textsuperscript{1}

Maximization of antimicrobial efficacy is a priority in the era of multidrug-resistant bacteria given the dearth of new antibiotics in production.\textsuperscript{2,3} The dramatic increase in bacterial resistance has led to increased recognition of inappropriate (ie, without in vitro activity against a microorganism) empirical treatment of infections in both community and hospital settings\textsuperscript{4,5} that dramatically affects mortality, morbidity,
and health care resources use. This article addresses the major factors that can lead to inappropriate empirical therapy and describes the effect of inappropriateness on the outcomes of critically ill patients with severe infections. Emerging evidence suggests that in vitro susceptibility is critical but not sufficient for achieving the best outcomes, and other factors have to be carefully considered. Therefore, it is important to revise the meaning of the expression appropriate antibiotic therapy by introducing the concepts of adequate and optimal. Hence, this review also briefly describes the factors that comprise the concepts of appropriate, adequate, and optimal initial antibiotic therapy.

**APPROPRIATE, ADEQUATE, AND OPTIMAL ANTIBIOTIC THERAPY**

Classically, the in vitro susceptibility of the causal pathogen was considered the reference aspect for antibiotic efficacy in the treatment of severe infections, and defined the concept of appropriate (or concordant) antibiotic therapy.\(^6\) However, this concept is becoming obsolete after the recognition that, although critical, the in vitro susceptibility is not enough for achieving optimal efficacy of antibiotic therapy.\(^7,8\) For example, Rello and colleagues\(^7\) showed that patients with methicillin-resistant *Staphylococcus aureus* (MRSA) ventilator-associated pneumonia (VAP) prescribed with vancomycin exhibited an excess mortality of 22.7%, which is unacceptable compared with the low mortality of methicillin-sensitive *S. aureus* (MSSA) VAP treated with β-lactams. This finding has led to adjustments in the definition of appropriateness, such as the 1 adopted recently by Vogelaers and colleagues,\(^9\) in which appropriate is defined as “in vitro susceptibility of the causative pathogen and clinical response to the agent administered.” In 2000, Kollef\(^10\) proposed a broader definition of adequate antibiotic therapy as “in vitro susceptibility together with proper dosing, proper interval administration, monitoring of drug levels when appropriate, and avoidance of unwanted drug interactions.” In 2006, our group proposed that antibiotic therapy could be classified as appropriate, adequate, and optimal on consideration of concrete factors that have a direct effect on achievement of optimal antibiotic efficacy.\(^11\) It follows that appropriate antibiotic therapy would include in vitro susceptibility and early administration, whereas adequate would refer to physicochemistry, and penetration and optimal would consist of pharmacokinetics/pharmacodynamics-driven dosage strategies.\(^11\) The Tarragona strategy was a strategy to manage VAP based on the concepts of appropriate, adequate, and optimal. This paradigm was intended to maximize the likelihood of prescribing the optimal antimicrobial in each case by controlling the factors likely to drive to inappropriateness of therapy.\(^12\) Fig. 1 represents the components of the antibiotic therapy optimization.

**CAUSES OF INAPPROPRIATE ANTIBIOTIC THERAPY**

Among many risks for suboptimal outcomes in critically ill patients, inappropriate empirical antibiotic therapy is a modifiable factor that clinicians must always consider. An extensive body of literature has shown that administration of inappropriate (or non-concordant) empirical therapy based on in vitro susceptibilities results in unfavorable clinical outcomes.\(^13–32\) The most common cause of inappropriate empirical antibiotic therapy is infection by a highly resistant pathogen.\(^33\) In the community and in-hospital settings, the incidence of infections resistant pathogens is rising worryingly.\(^2,33–35\) This increases the likelihood of administering inappropriate empirical therapy to patients not expected to be infected by resistant pathogens. In the hospital setting, the occurrence of infections caused by resistant bacteria is determined by the contribution of many factors, whose consideration is required for prediction of likely infective agents
in order to avoid inappropriate empirical therapies. The most relevant of these are described later.

**Prior Antibiotic Exposure**

The administration of previous antibiotic therapy has an important effect on the ecology of patient’s microflora, which can ultimately lead to infection with resistant strains of high-risk pathogens. In 1993, Rello and colleagues showed that the cause of VAP was significantly different in critically ill patients who received previous antibiotic therapy compared with patients who did not receive previous antibiotics. Previous antibiotic therapy resulted in a much higher incidence of infections caused by high-risk pathogens such as *Pseudomonas aeruginosa* or MRSA, with important increases in the mortality (up to 9 times higher). Other groups have confirmed this observation. If the previous antibiotics were broad-spectrum antibiotics, an independent association with high-risk pathogens has also been found. Knowledge about previous prescription of antimicrobial agents is paramount. This knowledge determines likely antibiotic resistances and guides therapy for present and further infectious episodes.

**Prolonged Length of Stay in the Hospital and Previous Hospitalization**

Prolonged length of stay (LOS) in the hospital and previous hospitalization also increase the likelihood of being colonized by resistant bacteria, which are likely to be the causal agents of subsequent severe infections. Chen and colleagues showed that patients who came from the community but had been recently discharged from the hospital had a higher risk of being infected by antimicrobial-resistant bacteria. In their study, previous carriage of antimicrobial-resistant bacteria in the past 360 days and previous stay in the ICU in the past 180 days were independent risk factors for antimicrobial-resistant bacteremia. Similarly, Bonten and colleagues studied the risk factors for being colonized and infected by vancomycin-resistant enterococci (VRE) in a cohort of critically ill patients and found that prolonged LOS in the hospital before the ICU increased the risk of colonization on ICU admission (odds ratio [OR] 4.65 when in-hospital LOS>3 days).
**Presence of Invasive Devices**

Endotracheal intubation, intravascular catheterization, and urinary catheterization in critically ill patients also increase the predisposition to acquiring infections by resistant bacteria. Richards and colleagues[^48] analyzed the data from a large ICU surveillance program and found that 87% of primary bloodstream infections were associated with central lines, 86% of nosocomial pneumonia was associated with mechanical ventilation, and 95% of urinary tract infections were associated with urinary catheters. The most common causal pathogens of these infections were coagulase-negative staphylococci with intravascular catheters, *P. aeruginosa* and *Acinetobacter* spp with endotracheal intubation and fungal infections by *Candida* spp with urinary catheters. Regarding respiratory infections, prolonged mechanical ventilation is also associated with a higher incidence of resistant pathogens in VAP. Trouillet and colleagues[^40] performed a study to determine risk factors for VAP caused by high-risk pathogens in critically ill patients and found that mechanical ventilation for more than 7 days was associated with a 6-fold increased probability of high-risk microorganisms.

**Local Susceptibilities**

Knowledge on local susceptibilities is paramount for avoiding the choice of inappropriate empirical therapy. There is extensive evidence in the literature that supports the belief that the spectrum of nosocomial pathogens likely to cause severe infections differs among different sites and even among different departments of the same institution.[^49]–[^51] A study by Rello and colleagues[^49] focused on the variations in the cause of VAP in critically ill patients from 4 different settings and reported significant variations in the incidence of high-risk pathogens, which particularly affected the number of pneumonias caused by MRSA, *P. aeruginosa* and *Acinetobacter* spp among sites. These results have been confirmed with hospital-acquired pneumonia (HAP) and VAP by other studies.[^50,52,53] A large European study described significant differences in the prevalence and antibiotic sensitivity patterns of the causal agents for nosocomial pneumonia in 27 ICUs from 9 European countries.[^50] For instance, Turkey and Greece had a high prevalence of *Acinetobacter* species in HAP/VAP episodes, whereas *P. aeruginosa* was commonly found in Italy and Portugal and Enterobacteriaceae species were common in Germany and Belgium. These data suggest that, instead of following general recommendations, antimicrobial prescribing practices for nosocomial infections should be based on up-to-date information of the pattern of multiresistant isolates from each institution. Although the 1996 American Thoracic Society guidelines for the management of nosocomial pneumonia failed to recognize local susceptibilities as a key factor for reducing the rate of inappropriate prescription,[^54] this recommendation was incorporated in the most recent edition of these guidelines as one of the most important factors to guide physicians’ antimicrobial selection.[^44]

**Admission Category and Underlying Diseases**

Admission category also determines the likely causal pathogens of an infection and should be considered when choosing empirical antimicrobials. For example, in VAP, causal agents in patients with trauma differ significantly from patients without trauma. MSSA is the predominant pathogen in comatose multiple-trauma patients,[^55] and nasal MSSA colonization at time of severe injury may increase the risk of MSSA pneumonia. The results of a large European study on HAP and VAP suggest that admission category drove physicians’ choice, because trauma
patients received more non–anti-*Pseudomonas* spp cephalosporins, whereas surgical patients were prescribed more aminoglycosides. Underlying diseases also have a causal role by predisposing the patient to be infected by specific organisms. For example, patients with chronic obstructive pulmonary disease are at increased risk for *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* infections, and cystic fibrosis increases the risk of *P aeruginosa* and *S aureus* infections.\(^{44}\)

### Colonization Pressure by Resistant Pathogens

It has been suggested that in ICUs, where antibiotic pressure is very high, increased colonization rates by high-risk pathogens may affect cross-acquisition of these microorganisms, probably because of an increased chance of physical contact between health care workers and patients colonized with resistant bacteria making any lapses in compliance of the infection control measures more likely to result in pathogen spread. The number of patients already colonized (colonization pressure) by resistant pathogens may be an important factor in increasing the probabilities of cross-colonization and cross-infection to other patients. This effect was shown by Bonten and colleagues\(^{57}\) with VRE. This group found that colonization pressure was the most important variable affecting VRE acquisition, and that the median time for a noncolonized patient to acquire VRE was significantly decreased with higher colonization pressures.\(^{57}\) Therefore, high colonization pressures by resistant pathogens in the ICU could be also a marker of suspicion for resistant pathogens to be found in nosocomial infections and to be targeted by empirical therapy.

### EFFECTS OF INAPPROPRIATENESS ON DIFFERENT KINDS OF INFECTION

Provision of appropriate empirical antimicrobials greatly affects morbidity and mortality in hospitalized patients. A large multicenter international study evaluated the effect of appropriateness on mortality and hospital LOS in a large cohort of hospitalized patients with severe infections, both community acquired and hospital acquired. Notably, inappropriate initial antibiotic treatment was prescribed to more than one-third of the patients, with similar proportions in the 3 investigational sites.\(^{31}\) All-cause 30-day mortalities were significantly higher in patients with inappropriate antibiotics (20.1% vs 11.8%, \(P = .001\)), and hospital LOS was increased by more than 2 days in the inappropriate treatment group (\(P = .024\)). Similarly, Kumar and colleagues\(^{32}\) recently published a study of 5715 patients in ICUs with septic shock, showing that mortality was higher when empirical antibiotic therapy was inappropriate (52.0%) than when appropriate (10.3%). Inappropriateness was confirmed to be independently associated with mortality by multivariate logistic regression (OR, 8.99; 95% CI, 6.60–12.23; \(P<.0001\)). Moreover, inappropriateness was significantly associated with the isolated microorganism, fungal species being the microorganisms that were most frequently treated inappropriately (56.4% of the cases),\(^{32}\) followed by gram-positive organisms (22.2%).

Regarding other concrete clinical scenarios, the effect of inappropriateness on outcomes has also been shown in a variety of infectious causes, detailed later.

### Nosocomial Pneumonia

Pneumonia is the most frequent nosocomial infection described in critically ill patients. Rates of pneumonia are considerably higher among patients in the ICU than in wards, and the risk for developing pneumonia is higher in intubated patients receiving mechanical ventilation.\(^{56}\) However, despite extensive research and clinical experience
with this disease, controversy regarding optimal management still exists. Because of the unacceptably high mortality and morbidity of this complication,\textsuperscript{59} maximization of the effectiveness of the therapeutic arsenal is mandatory. Patients with a diagnosis of nosocomial pneumonia who receive appropriate antibiotic therapy are more than twice as likely to survive.\textsuperscript{13,14} The effects of inappropriate antibiotic therapy on patient outcomes and resources use are well described in the literature. Fig. 2 summarizes the results of some of the most relevant studies in VAP.

Rello and colleagues\textsuperscript{14} found that, in patients with VAP, both crude and attributable mortalities decreased significantly in patients who received appropriate empirical antibiotics (63.0\% vs 41.5\% for crude and 37.0\% vs 15.4\% for attributable mortality). Luna and colleagues\textsuperscript{29} assessed the appropriateness of therapy based on the results of bronchoalveolar lavage (BAL) cultures in critically ill patients with nosocomial pneumonia, and reported similar findings (91.2\% vs 37.5\% mortality in inappropriate vs appropriate therapy). Other studies have confirmed these results with VAP and HAP.\textsuperscript{18,19,27,28} Regarding LOS in the ICU, Dupont and colleagues\textsuperscript{19} showed that inappropriate mortality resulted in more ICU days (12 ± 11 days vs 20 ± 24 days, $P = .01$). A recent meta-analysis on the effect of inappropriate antibiotic therapy on mortality in patients with VAP has been published.\textsuperscript{60} The investigators pooled the results of 10 clinical studies on patients with VAP and found that, both when using an unadjusted and an adjusted model, the odds ratio for death increased greatly when inappropriate therapy was prescribed (OR, 2.34; 95\% CI, 1.51–3.63 for unadjusted data, and OR, 3.03; 95\% CI, 1.12–8.19 for adjusted data). In these studies, most of the episodes of inappropriate treatment were caused by bacterial resistance to the empirically administered antibiotics rather than the presence of atypical pathogens.\textsuperscript{14,16} High-risk pathogens such as \textit{P. aeruginosa}, \textit{Acinetobacter} spp, and MRSA are common in VAP and HAP\textsuperscript{50} and should be targeted when risk factors are present to minimize the chances of inappropriateness and bad outcomes.

The Infectious Diseases Society of North America, the American College of Chest Physicians, the Society of Critical Care Medicine, and the American Thoracic Society have recently published a position paper with recommendations for the design of

![Fig. 2](image)
further clinical trials for HAP and VAP. The investigators emphasize that clinical trials for HAP and VAP usually exclude patients with infections caused by organisms resistant to standard comparator drugs from enrollment. These patients would be more likely to receive inappropriate empirical therapy with the comparator drug. Therefore, new antibacterial drugs will probably not be tested in the scenarios that would benefit most from the new treatment and achieve superior efficacy compared with the gold standard. However, extreme gram-negative drug resistance (XDR) has created a situation in which superiority trials can be performed, because the investigational drug can show clinical benefit compared with the standard therapy because of the lack of an approved alternative to which the pathogen is susceptible. These kinds of studies are desirable and should be supported to advance clinical therapy and to improve treatment of HAP and VAP.

**Bloodstream Infections**

Bloodstream infections (BSI) are among the most serious complications found in critically ill patients, with high associated mortality, morbidity, and health care expenses. The Center of Disease Control’s National Nosocomial Infections Surveillance System has reported that BSI account for up to 20% of the nosocomial infections in critically ill patients, with approximately 80% of those related to the use of invasive devices such as intravascular catheters. The spectrum of causal agents that frequently cause BSI in the ICU is broad, and mainly comprises staphylococci and gram-negative bacteria with coagulase-negative staphylococci by far the most frequent single pathogen. However, the incidence of infections caused by high-risk gram-negative bacilli, gram-positive cocci, and nonbacterial pathogens has been rising during the 3 past decades, even in the community setting, with high rates of *Enterococcus* spp, MRSA, *P aeruginosa*, and *Candida* spp that may increase the likelihood of provision of inappropriate empirical antibiotic therapy. Moreover, certain clinical scenarios increase the likelihood that specific pathogens will need to be covered. For instance, immunocompromised patients, patients who have received red blood cell transfusions, patients who have undergone abdominal surgery, who are receiving total parenteral nutrition, are colonized by yeasts, or with femoral catheters are more likely to have BSI by *Candida* spp, and patients with femoral or jugular lines, with severe sepsis, or with septic shock are more likely to be infected by gram-negative bacteria.

Many studies have focused on the effect of inappropriateness on outcomes of BSI in critically ill patients, and have shown that patients who receive inappropriate empirical antibiotics are at more than a 2-fold risk of dying. Fig. 3 summarizes the findings of some of the studies focused on mortality in BSI depending on appropriateness of empirical treatment.

Valles and colleagues studied the prognosis of community-acquired BSI in a cohort of critically ill patients from 30 Spanish ICUs and reported that the factor with the greatest effect on mortality was administration of inappropriate empirical antibiotic therapy (mortality 69.4% vs 37% in inappropriate vs appropriate, OR for mortality with inappropriate empirical antibiotic 3.23, 95% CI 1.52–6.82), especially when vasopressors were required. Similar findings were reported when studying hospital-acquired BSI. Leibovici and colleagues studied the evolution of nosocomial bacteremia in 3413 patients and found that the fatality rate in patients given appropriate treatment was 20%, whereas in patients given inappropriate treatment it was 34% (*P* = .0001, OR 2.1, 95% CI 1.8–2.4). They also reported significant differences in LOS in the hospital between groups. The hospital LOS for patients who survived was 9 days (range 0–117 days) for patients who received appropriate empirical
antibiotics, and 11 days (range 0–209 days) for patients given inappropriate antibiotics ($P = .0001$). For patients who died, the median hospital LOS was 5 days (range 0–120 days) for those given appropriate antibiotic treatment, and 4 days (range 1–83 days) for those given inappropriate treatment ($P = .03$). Schramm and colleagues performed a retrospective cohort analysis of the influence of appropriate therapy on outcomes of sterile-site infections by hospital-acquired MRSA and community-acquired MRSA (CA-MRSA). They reported statistically higher hospital mortality in patients receiving inappropriate initial antimicrobial treatment within 24 hours of a positive culture than for those receiving appropriate initial treatment (26.1% vs 16.6%; $P = .015$). The investigators recommended initial empirical antimicrobial treatment regimens targeting MRSA in patients at risk for this infection or in a high-incidence area. Kumar and colleagues reported that appropriate therapy in primary bloodstream infections without an obvious clinical source in patients with septic shock was associated with a 17.6-fold better survival than inappropriate initial therapy (47.5% vs 2.7%, respectively). A recent meta-analysis pooled the data from 22 clinical studies and showed an adjusted OR for mortality of 2.28 (95% CI 1.43–3.65) when empirical antibiotics were inappropriate.

Severe Skin and Soft Tissue Infections

Skin and soft tissue infections (SSTI) can result in critical illness and require ICU admission. *S aureus* and group A streptococci are the most common causal agents of SSTI, followed by other bacteria such as *Clostridium* spp. Antibiotics are a crucial element in the management of SSTI. The selection of the appropriate antibiotic is driven by many factors, especially after the increase in the rate of infections caused by CA-MRSA. In the United States, CA-MRSA has been reported to be the causal pathogen of 59% of the SSTI that arrive at emergency departments.

Inappropriate empirical antibiotic therapy has significantly effects in the resolution of SSTI. Chuck and colleagues designed an algorithm for the empirical treatment...
of severe SSTI in the emergency department, where they prompted physicians to use antibiotics active against CA-MRSA for complicated infections. When they analyzed outcome data regarding appropriateness of treatment, they reported that patients who underwent surgical drainage and received appropriate antibiotics had much better clinical cures (100%) compared with those who only underwent drainage but received inappropriate empirical therapy (33%).\textsuperscript{71} Ruhe and colleagues\textsuperscript{72} retrospectively studied the resolution of noncomplicated SSTI in 492 adult patients with CA-MRSA and found that 95% of patients with appropriate antibiotic, versus 87% with inappropriate antibiotic, resolved satisfactorily from the infection ($P = .01$). Multivariate analysis showed failure to initiate appropriate antibiotics within 48 hours as the only factor determining treatment failure (OR 2.80, 95% CI 1.26–6.22).

**Meningitis**

Bacterial meningitis is caused by severe infections that require prompt administration of effective antibiotics. Community-acquired bacterial meningitis has a high rate of an unfavorable outcome in adults (34%), with the most common causal pathogens being *Streptococcus pneumoniae*, *Neisseria meningitides*, and *Listeria monocytogenes*.\textsuperscript{73} Pneumococcal meningitis leads to higher death rates and more unfavorable outcomes than meningococcal pneumonia.\textsuperscript{73} Because of the increase in the incidence of strains of *S pneumoniae* resistant to penicillin in many countries such as the United States,\textsuperscript{74} an increased risk of inappropriateness of empirical treatment has been identified. Accordingly, high mortalities have been observed in meningitis episodes caused by penicillin-resistant pneumococcal strains. A multicenter study of 156 consecutive adults hospitalized for pneumococcal meningitis shown that 38% of the identified strains were nonsusceptible to penicillin G. The multivariate analysis identified isolation of a nonsusceptible pneumococcus strain as one of the factors that most increased the OR for death (OR 6.83, 95% CI 2.94–20.8, $P<.0004$), together with delays of more than 3 hours in the administration of antibiotics (OR 14.12, 95% CI 3.93–50.9; $P<.0004$).\textsuperscript{75} Other studies have focused on the effect of inappropriateness on outcomes of severe meningitis caused by other pathogens, with compelling results.\textsuperscript{76–78} Lu and colleagues\textsuperscript{76} studied the prognostic factors of gram-negative meningitis in 77 patients and found that 100% of patients who received inappropriate therapy died because of the infectious episode, compared with 38% mortality with appropriate therapy. Inappropriate empirical antibiotics resulted in an independent predictor of higher mortality in the logistic regression model.\textsuperscript{76} The same group reported similar results with *Klebsiella* spp meningitis in adults during a 13-year period (100% death in inappropriate vs 24.4% in appropriate antibiotics).\textsuperscript{78}

**ADEQUATE ANTIBIOTIC THERAPY**

The terms antimicrobial and antibiotic include many compounds that considerably differ in physicochemistry. Chemically, the distribution coefficient between water and lipids classifies a molecule as hydrophilic or lipophilic. This property determines the tissues to which drug molecules will preferentially distribute. Hydrophilic drugs will distribute mainly in the intravascular and extracellular body water, whereas lipophilic antibiotics can cross barriers and distribute intracellularly and into the lipid tissues.\textsuperscript{79} This characteristic determines the amount of drug that will be able to reach certain organs, which is directly proportional to the pharmacologic effect. For example, to reach tissues and organ systems such as the lung, the central nervous
system, or the bone marrow, many physiologic barriers must be crossed. These barriers may reduce the rate and extent of antibiotic distribution, and concentrations achieved at the target site may be suboptimal. The glycopeptide vancomycin is an example of an antimicrobial that can exhibit suboptimal penetration into key target organs. Vancomycin is highly hydrophilic and has been shown to penetrate poorly into lung tissue and pulmonary epithelial lining fluid (ELF) (5:1 blood/tissue and 6:1 blood/ELF ratio).\(^80,81\) Another case is ceftriaxone, which achieves concentrations in the central nervous system that are between 1.5% and 2.5% of the plasma concentrations as a consequence of its hydrophilicity and its high level of protein binding.\(^82\) Hence, it is important to take into account the target organ system or tissue where the infection is located, and select antimicrobials likely to achieve therapeutic concentrations at the target site.

**OPTIMAL ANTIBIOTIC THERAPY**

Optimal antibiotic therapy includes the consideration of factors beyond susceptibility, minimum inhibitory concentration (MIC) of the bacteria, and tissue concentrations of the drug. Selection of the optimal dosage is complex because specific drug and patient characteristics must be considered individually and in aggregate. First, the pharmacokinetic/pharmacodynamic behavior of each antimicrobial and the particular physiology of critically ill patients must be taken into account.\(^83\) Different antimicrobials exhibit different bacterial killing characteristics associated with certain pharmacodynamic indices. Antibiotics whose mechanism of action is through the inhibition of nucleic acid or protein synthesis have a postantibiotic effect (PAE), with inhibition of bacterial growth even when concentrations are lower than the MIC.\(^84\) For this reason, administration of high doses of these drugs once or twice daily is generally preferred to multiple and frequent dosing (concentration-dependent killing). In contrast, antibiotics that inhibit the bacterial wall synthesis, such as \(\beta\)-lactams, kill bacteria more slowly and do not have a clinically significant PAE. Accordingly, such drugs must maintain a concentration at the infection site that is greater than the MIC of the pathogen for a certain period of time to achieve optimal effectiveness (time-dependent killing).\(^84\) Therefore, dosage regimens must be adjusted to these specific pharmacodynamic properties to optimize bacterial killing.

In addition, critically ill patients exhibit several physiologic alterations that may affect antimicrobial pharmacokinetics and result in underdosing. The clinical management of hypotension or septic shock is likely to include fluid resuscitation and inotropes, leading to early increased renal blood flow and augmented renal clearances,\(^85,86\) which translates into faster elimination of hydrophilic drugs. In this circumstance, higher-than-standard daily doses of the antimicrobial may be required. Also, because of capillary leakage and hypoalbuminemia, among other causes,\(^87,88\) the volume of distribution of many hydrophilic antimicrobials is likely to increase greatly.\(^89–91\) Consequently, increased loading doses could be necessary to achieve therapeutic concentrations on the first day of therapy.

**RECOMMENDATIONS**

As detailed earlier, inappropriate empirical therapy is a modifiable determinant of poor outcomes that clinicians must address aggressively. Broad-spectrum antibiotics, in monotherapy or in combination where appropriate, should be prescribed empirically when high-risk pathogens are suspected. Likely pathogens should be targeted depending on risk factors described previously. Local susceptibility surveillance data should be updated regularly to keep clinicians aware of local resistance patterns.
Once culture results are available, reassessment of the prescribed antimicrobial regimen with potential de-escalation to narrower-spectrum drugs is recommended to reduce the antibiotic selection pressure and decrease the development of antibiotic resistance.\textsuperscript{92,93} Development of acute-care antimicrobial bundles could improve the rate of appropriate prescription of antibiotics at the bedside, and may be the next major step in the process of optimization of infection management.\textsuperscript{94} A care bundle for the management of VAP has recently been proposed by our group. The components of this bundle are summarized in Box 1.\textsuperscript{95} This review emphasizes the importance of administering early and broad-spectrum antimicrobials with consideration of risk factors and local susceptibilities in order to avoid inappropriateness of therapy. Afterward, de-escalation based on culture results and shortening of the duration of therapy where possible are strongly recommended.\textsuperscript{96} Further advances in the creation and validation of management care bundles for severe infections in the ICU are required. Moreover, therapeutic drug monitoring (TDM) of peak and/or trough concentrations would be helpful in the optimization of antibiotic therapy. Knowledge of trough concentration values allows clinicians to assess whether dosing leads to concentration/time profiles for optimal therapy, and to make appropriate adjustments as needed to reach therapeutic values. Drugs such as glycopeptides and aminoglycosides are regularly monitored in the clinical setting; however, the application of TDM principles to β-lactams (the most prescribed class of antibiotics) would be desirable because of the great variations in the pharmacokinetics of these drugs in critically ill patients.\textsuperscript{96} A recently published paper prospectively used TDM for evaluating whether β-lactam dosing led to optimal levels in patients in ICUs. This study showed that 50.4\% of patients were underdosed at the first TDM sample, requiring dose increases.\textsuperscript{97} More prospective work on the potential and usefulness of using TDM as a strategy for optimizing antibiotic dosing of β-lactams in patients in ICUs is highly recommendable.

Box 1

<table>
<thead>
<tr>
<th>The domains of the care bundle for the management of VAP in the ICU</th>
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<tbody>
<tr>
<td>VAP management care</td>
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<tr>
<td>Bundle VAP diagnosis</td>
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<tr>
<td>Early chest radiograph with interpretation by an expert within 1 hour</td>
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<tr>
<td>Immediate reporting of the Gram stain findings and cells from the respiratory secretions analysis</td>
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<tr>
<td>VAP treatment</td>
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<tr>
<td>Immediate administration of broad-spectrum antibiotics following microbiological sampling</td>
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<tr>
<td>Empirical therapy based on assessment of assessment local surveillance data and risk factors for resistant bacteria</td>
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<tr>
<td>De-escalation of antibiotics in responding patients once culture results are available</td>
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<tr>
<td>Assessment of response to treatment within 72 hours</td>
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<td>Short therapy duration (8 days) if patient is on an appropriate regimen and not infected by a multidrug-resistant pathogen</td>
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</table>

SUMMARY

The pathophysiology of severe infections and the complexity of nosocomial pathogens make the optimization of the antimicrobial management of severe infections extremely difficult. In critically ill patients with severe infections, inappropriate empirical treatment is often associated with the presence of microorganisms resistant to the usual antibiotics. Such resistant organisms are increasingly being found in both community-acquired and nosocomial infections. Previous receipt of antibiotics, prolonged LOS in the hospital, admission category, local susceptibilities, colonization pressure, and presence of invasive devices increase the likelihood of being infected by resistant pathogens. Administration of inappropriate empirical antibiotics significantly worsens outcomes and increases health care expenses in many severe infections such as nosocomial pneumonia, meningitis, SSTI, and bloodstream infections. These and other serious infections require appropriate empirical antimicrobial therapy, ideally with an agent that covers both gram-positive and gram-negative pathogens. Clinicians should include local antimicrobial resistance pattern data (antibiograms) and known risk factors for high-risk pathogens in their decision making regarding empirical therapy in order to improve quality of care and outcomes. Moreover, emerging evidence suggests that appropriate empirical therapy is critical but not sufficient to achieve the best patient outcomes. Consideration of issues beyond in vitro susceptibility, such as antimicrobial physicochemistry, tissue penetration, and pharmacokinetic/pharmacodynamic-driven dosing is required for the optimization of antimicrobial use in the ICU. Further clinical research on this area is strongly recommended.

REFERENCES


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