Inadequate Antimicrobial Treatment: An Important Determinant of Outcome for Hospitalized Patients

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Inadequate antimicrobial treatment, generally defined as microbiological documentation of an infection that is not being effectively treated, is an important factor in the emergence of infections due to antibiotic-resistant bacteria. Factors that contribute to inadequate antimicrobial treatment of hospitalized patients include prior antibiotic exposure, use of broad-spectrum antibiotics, prolonged length of stay, prolonged mechanical ventilation, and presence of invasive devices. Strategies to minimize inadequate treatment include consulting an infectious disease specialist, using antibiotic practice guidelines, and identifying quicker methods of microbiological identification. In addition, clinicians should determine the prevailing pathogens that account for the community-acquired and nosocomial infections identified in their hospitals. Clinicians can improve antimicrobial treatment by using empirical combination antibiotic therapy based on individual patient characteristics and the predominant bacterial flora and their antibiotic susceptibility profiles. This broad-spectrum therapy can then be narrowed when initial culture results are received. Further study evaluating the use of antibiotic practice guidelines and strategies to reduce inadequate treatment is necessary to determine their impact on patient outcomes.

There is a general consensus in the medical community that antimicrobial resistance in the hospital setting has emerged as an important variable that influences patient outcomes and overall resource utilization [1–3]. Hospitals worldwide are faced with increasingly rapid emergence and spread of antibiotic-resistant bacteria. Both antibiotic-resistant gram-negative bacilli and gram-positive bacteria are reported as important causes of hospital-acquired infections [4, 5]. In many cases, few antimicrobial agents remain for effective treatment, particularly with methicillin-resistant and vancomycin-tolerant *Staphylococcus aureus* and gram-negative bacteria producing extended-spectrum β-lactamases with resistance to multiple other antibiotics [6–8]. A number of recent editorials and reviews have called for increased efforts to intensify current infection control practices aimed at reducing the emergence and dissemination of infections due to antibiotic-resistant bacteria [1, 9, 10]. In addition, the development of new antimicrobial agents directed against these emerging pathogens has recently accelerated with the clinical evaluation of a number of promising agents [11–13].

One of the consequences of greater antimicrobial resistance is an increased recognition of inadequate antimicrobial treatment of infections in both community and hospital settings [14, 15]. The problem of inadequate antimicrobial treatment of infections in hospitalized patients, particularly in specialized areas of the hospital, has become an important focal point for the emergence of infections due to antibiotic-resistant bacteria. Intensive care units, oncology/bone marrow transplantation wards, and dialysis units are some of the primary areas associated with inadequate antimicrobial treatment [4, 5, 16–19]. The increasing presence of infections due to antibiotic-resistant bacteria is likely related to numerous pressures that play a role in escalating the emergence of antibiotic-resistant bacteria in these units. These pressures include the following: frequent use of broad-spectrum antibiotics; crowding of patients with high levels of disease acuity within relatively small specialized areas of the hospital; reductions in nursing and support staff due to economic pressures, which increase the likelihood of person-to-person transmission of antibiotic-resistant bacteria; and presence of more chronically and acutely ill patients who require prolonged hospitalizations and often harbor antibiotic-resistant bacteria [20–22].

Definition of Inadequate Antimicrobial Treatment

Pharmacological treatment of an identified infection should include the administration of antimicrobials with demonstrated bacteriostatic or bactericidal activity against the identified etiologic agents of infection. Use of antimicrobial treatment without activity against the identified pathogen can be considered inadequate. Inadequate antimicrobial treatment of infection re-

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cently was defined, for clinical research purposes, as follows: microbiological documentation of an infection (i.e., a positive culture result) that was not being effectively treated at the time of its identification; absence of antimicrobial agents directed against a specific class of microorganisms (e.g., absence of therapy for fungemia due to *Candida albicans*); and/or administration of an antimicrobial agent to which the microorganism responsible for the infection was resistant (e.g., empirical oxacillin treatment of pneumonia subsequently attributed to methicillin-resistant *S. aureus* based on appropriate culture results) [23]. In addition, the complete absence of antimicrobial treatment of a microbiologically confirmed infection was considered to represent inadequate antimicrobial treatment.

However, inadequate antimicrobial treatment can be defined more broadly. Clinicians must ensure that antibiotic administration follows certain minimal requirements, such as proper dosing, proper interval administration, monitoring of drug levels when appropriate, and avoidance of unwanted drug interactions. Lack of adherence to these minimal requirements can result in suboptimal antibiotic concentrations, which increase the likelihood that antibiotic resistance will occur and the chance that inadequate antimicrobial treatment will be administered [24–27].

Risk Factors for Antibiotic Resistance and Inadequate Antimicrobial Treatment of Infections

Investigators have demonstrated a close association between the use of antibiotics and the emergence of antibiotic resistance in both gram-negative and gram-positive bacteria [28–32]. The recent experience with antibiotic cycling or scheduled antibiotic class changes also demonstrates how rapidly antibiotic-resistant bacteria can emerge within hospitals as patterns of antimicrobial use change [33–35]. Trouillet et al. [36] examined 135 consecutive episodes of ventilator-associated pneumonia (VAP); 77 (57%) of these episodes were caused by potentially antibiotic-resistant bacteria (methicillin-resistant *S. aureus, Pseudomonas aeruginosa, Acinetobacter baumannii,* or *Stenotrophomonas maltophilia*). According to logistic regression analysis, mechanical ventilation for ⩾7 days, prior antibiotic use, and prior use of broad-spectrum antibiotics (third-generation cephalosporin, fluoroquinolone, and/or imipenem) are associated with the development of VAP due to antibiotic-resistant pathogens. This investigation confirms that previous antibiotic exposure is an important risk factor for nosocomial infections due to antibiotic-resistant bacteria [37–39]. In addition, the identification of specific risk factors for the occurrence of infections due to antibiotic-resistant bacteria, such as prior antimicrobial exposure, provides guidance for the development of potential interventions aimed at the reduction of such infections [40].

In addition to prior antibiotic exposure, other risk factors are associated with the emergence of infections due to antibiotic-resistant bacteria. Prolonged length of stay in the hospital appears to predispose to infection with antibiotic-resistant bacteria [36]. This risk factor may be due, in part, to the greater likelihood of patients becoming colonized with such bacteria (from either horizontal nosocomial transmission or endogenous emergence of resistance) the longer they remain in the hospital. Thus, the pathogens are less likely to be eradicated, and patients are more likely to receive prolonged antimicrobial therapy. Similarly, the presence of invasive devices, such as endotracheal tubes, intravascular catheters, and urinary catheters, in critically ill patients also predisposes to infection with antibiotic-resistant bacteria (figure 1) [41].

Increasingly, patients are being admitted to hospitals with infections due to antibiotic-resistant bacteria, thus increasing the likelihood that inadequate antimicrobial treatment will be administered to them. The identification of methicillin-resistant *S. aureus* colonization and infection, which occur in children hospitalized without identifiable risk factors for such infections (e.g., prior hospitalization or antimicrobial exposure), is among the most worrisome of these recent observations [42, 43]. However, adult patients admitted to intensive care units also are increasingly being recognized as having colonization or infection with antibiotic-resistant bacteria [44, 45]. Identified risk factors for colonization or infection with antibiotic-resistant bacteria at the time of intensive care unit admission include prior hospitalization, previous antimicrobial exposure, and increasing severity of illness [44, 45]. This trend is worrisome because infections due to antibiotic-resistant bacteria may be associated with higher attributable mortality rates than are infections caused by more-susceptible bacterial strains [46–49].

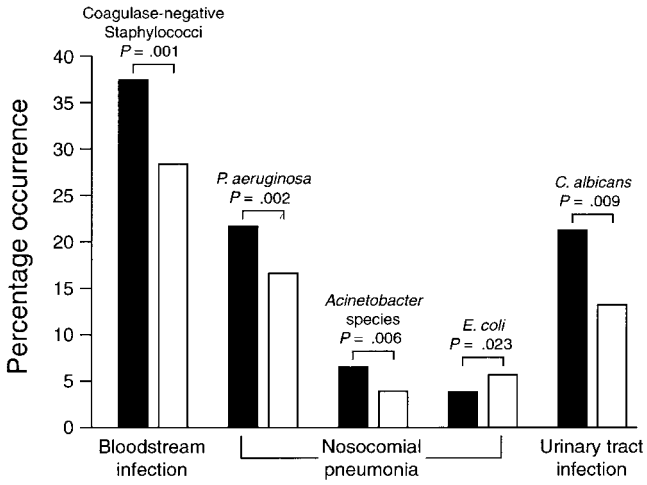

Figure 1. Occurrence of specific etiologic agents of nosocomial infections according to infection site and presence of corresponding underlying invasive device (i.e., central venous catheter for bloodstream infection, endotracheal tube for nosocomial pneumonia, and urinary tract catheter for urinary tract infection). *Black bar,* invasive device present; *white bar,* invasive device absent.

Bloodstream Infections

Bloodstream infections are among the most serious infections acquired by hospitalized patients who require intensive care. The coexistence of a pathogen population that has an ever-increasing resistance to many antibiotics and a patient population characterized by increasingly complex clinical problems has contributed to increased bloodstream infections (particularly due to antibiotic-resistant gram-positive bacteria) [50]. Antibiotic resistance may be associated with administration of inadequate antimicrobial therapy for bloodstream infections, particularly hospital-acquired bloodstream infections (which are associated with higher hospital mortality rates) [51–57]. Some investigations, however, have not found higher mortality rates with the presence of bacteremia due to antibiotic-resistant organisms, particularly vancomycin-resistant enterococcal bacteremia compared with vancomycin-susceptible enterococcal bloodstream infections [58, 59]. Nevertheless, the problem of bacteremia due to antibiotic-resistant organisms is increasing both in the hospital setting and in the community [60]. Given the current trend of greater severity of illness in hospitalized patients, it can be expected that infections due to antibiotic-resistant bacterial strains will be associated with higher morbidity and mortality rates, particularly when inadequate empirical antimicrobial treatments are administered [23].

Leibovici et al. [51] found that the hospital mortality rate was significantly lower for patients with bloodstream infections who received adequate antimicrobial treatment than for those who received inadequate treatment (20% vs. 34%, respectively; $P < .001$). Similarly, Weinstein et al. [53] demonstrated that the mortality rate was lowest among patients who received adequate antimicrobial treatment throughout the course of bloodstream infection. Isolation of multidrug-resistant *Enterobacter* species in initial cultures of blood specimens from infected patients has been associated with a higher mortality rate than has isolation of a more susceptible *Enterobacter* species (32% vs. 15%, respectively; $P = .03$) [57]. The emergence of infection due to multidrug-resistant *Enterobacter* species was associated with prior administration of third-generation cephalosporins. Multivariate analysis demonstrated that inadequate antimicrobial treatment is an independent risk factor of mortality for patients with bloodstream infections [51, 54]. Identified risk factors for the administration of inadequate antimicrobial treatment to patients with bloodstream infections include prior administration of antimicrobial therapy, presence of intravascular catheters, and infection due to antibiotic-resistant pathogens (e.g., *Candida* species, methicillin-resistant *S. aureus,* vancomycin-resistant enterococci, and coagulase-negative staphylococci) [41, 57, 61].

Nosocomial Pneumonia and VAP

Pneumonia is the most commonly described nosocomial infection in patients who require intensive care, occurring predominantly in those requiring mechanical ventilation at a rate of 1%–3% per day [62]. The estimated prevalence of nosocomial pneumonia within critical care units ranges from 10% to 65%, with case-fatality rates of >20% in most reported studies [63]. Despite improvements in the diagnosis, treatment, and prevention of nosocomial pneumonia, it remains a primary cause of hospital mortality [64, 65]. Nosocomial pneumonia that occurs within 48 h of hospital admission is usually attributed to antibiotic-susceptible pathogens, including *Haemophilus influenzae,* methicillin-susceptible *S. aureus,* and *Streptococcus pneumoniae,* whereas late-onset nosocomial pneumonia is frequently attributed to antibiotic-resistant pathogens, such as methicillin-resistant *S. aureus, P. aeruginosa,* and *Acinetobacter* species [66, 67]. Inadequate treatment of nosocomial pneumonia, particularly in the intensive care unit setting, is increasingly being recognized as a potential cause of increased patient morbidity.

Treatment of nosocomial pneumonia is usually supportive, along with the administration of antibiotics. The selection of antimicrobial agents active against the microorganisms associated with nosocomial pneumonia seems to be an important determinant of hospital mortality. Luna et al. [68] studied 132 patients with clinically suspected nosocomial pneumonia who required mechanical ventilation. Fifty patients for whom bronchoalveolar lavage (BAL) fluid cultures were positive received empirical antibiotic treatment before results of BAL fluid cultures were obtained. The mortality rate among the 16 patients who received adequate antibiotic treatment, as defined by the BAL fluid cultures, was significantly lower than that among the 34 patients who received inadequate antibiotic treatment (37.5% vs. 91.2%, respectively; $P < .001$). Alvarez-Lerma [69] evaluated the appropriateness of antimicrobial treatment for 430 treated patients with VAP; the attributable mortality rate of VAP was significantly higher among patients who received inadequate initial antimicrobial treatment than among patients who received adequate initial treatment (24.7% vs. 16.2%, respectively; $P = .039$). Similarly, Rello et al. [70] found that the crude mortality rate (63.0% vs. 41.5%, respectively; $P = .06$) and the attributable mortality rate of VAP (37.0% vs. 15.6%, respectively; $P < .05$) were significantly higher among patients with VAP who received inadequate initial antimicrobial treatment than among those who received adequate antibiotic treatment. Our own group has confirmed these findings for patients with VAP who were diagnosed by using BAL fluid cultures as well as clinical criteria alone [45, 71].

The most common pathogens associated with the administration of inadequate antimicrobial treatment to patients with VAP are shown in figure 2 [68–71]. Most episodes of inadequate antimicrobial treatment were attributed to potentially antibiotic-resistant gram-negative bacteria, including *P. aeruginosa, Acinetobacter* species, *Klebsiella pneumoniae,* and *Enterobacter* species. *S. aureus* was the second most common cause of inadequate treatment, with most strains being methicillin resistant. Anaerobic bacteria seem to be relatively uncommon eti-

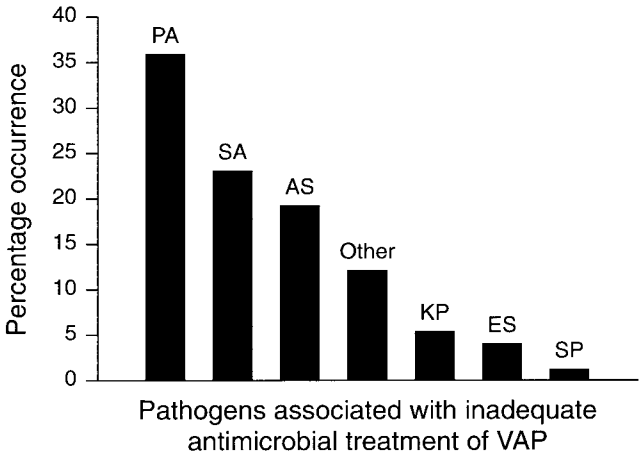

Figure 2. Ranking of bacterial pathogens associated with the administration of inadequate antimicrobial treatment of ventilator-associated pneumonia (VAP). AS, *Acinetobacter* species; ES, *Enterobacter* species; KP, *Klebsiella pneumoniae;* PA, *Pseudomonas aeruginosa;* SA, *Staphylococcus aureus;* SP, *Streptococcus pneumoniae;* other, *Haemophilus influenzae, Escherichia coli, Proteus mirabilis, Serratia marcescens,* and *Legionella* species.

ologic agents of nosocomial pneumonia or VAP and, therefore, are not likely to be a primary factor in the use of inadequate antimicrobial treatment [72, 73].

Strategies to Reduce the Administration of Inadequate Antimicrobial Treatment

Six clinical strategies that have been employed to improve the administration of antimicrobial treatment in the hospital setting are summarized in table 1. These strategies have been used to evaluate the administration of inadequate antimicrobial treatment as either the primary or secondary outcome of the intervention.

Infectious disease specialists. Several investigations have demonstrated the beneficial impact of consulting an infectious disease specialist on patient outcomes. Byl et al. [74] evaluated 428 episodes of bacteremia in a teaching hospital. Empirical antimicrobial treatment was appropriate for 78% of the episodes of bacteremia treated by infectious disease specialists compared with 54% treated by other physicians ($P < .001$). Inappropriateness of the empirical antimicrobial regimen was found to be independently associated with a higher mortality rate. Similarly, the occurrence of vancomycin-resistant enterococcal infections was found to decrease significantly when an enhanced infection control strategy was employed that included having an infectious disease specialist evaluate patients receiving treatment with antimicrobial agents [75]. Although the occurrence of inadequate antimicrobial treatment was not evaluated in this study, reducing rates of infection due to antibiotic-resistant bacteria would be expected to decrease the occurrence of inadequate treatment.

Antibiotic practice guidelines. The potential benefits of antibiotic use guidelines in the hospital setting have been demonstrated by the experience of Latter Day Saints Hospital in Salt Lake City, which employs a computerized system that guides clinicians' use of antibiotics. This system has been successfully employed to identify and minimize the occurrence of adverse drug effects caused by antibiotic administration [76]. Moreover, the use of an automated antimicrobial prescribing system has been shown to reduce the occurrence of inadequate empirical antibiotic administration as compared with individual physician prescribing practices [77]. With this prescribing system, physicians identify the patient and the infection site; the computer accesses the patient's medical record and uses patient- and infection-specific information to determine the most likely pathogens, which reflect the most common pathogens identified during the previous 5 years and the most recent 6 months. The computer then provides 5 antimicrobial regimens most likely to be effective against all the pathogens and suggests an appropriate regimen for the patient. Similarly, Leibovici et al. [78] developed a problem-oriented data-based decision support system that significantly reduced the unnecessary use of antibiotics and inadequate antibiotic administration, particularly for patients infected with multidrug-resistant gram-negative isolates, enterococci, and *S. aureus.* Finally, antibiotic or disease-specific interventions, which employ guidelines for antibiotic utilization in addition to physician education and professional detailing, have been successfully employed in the outpatient setting to reduce the unnecessary use of antibiotics [79, 80]. Similar types of interventions could be developed for in-hospital use also with the goals of reducing antibiotic misuse and overuse and decreasing the administration of inadequate antimicrobial treatment [81].

Combination Antibiotic Therapy

The use of combination antimicrobial treatment as a strategy to reduce the emergence of bacterial resistance, as has been employed for *Mycobacterium tuberculosis,* has been proposed [82]. However, conclusive data that combination antibiotic therapy for nosocomial bloodstream infections prevents the subsequent emergence of antibiotic resistance are lacking [83, 84]. Nevertheless, there is some indirect evidence that supports the

Table 1. Strategies to reduce the administration of inadequate antimicrobial treatment in the hospital setting.

Consultation by an infectious disease specialist
Antibiotic practice guidelines
Combination antimicrobial treatment
Scheduled changes or cycling of antimicrobial agents
More rapid microbiological identification
Reduction of the prevalence of antimicrobial resistance in both the community and the hospital setting

use of combination antimicrobial therapy to reduce the emergence of antimicrobial resistance. Mathematical models suggest that combination antibiotic therapy will always be superior to single antibiotic use in preventing resistance [85]. Moreover, the simultaneous exposure of portions of the population to different antibiotics will likely result in less resistance than the sequential use of antibiotics in the entire population. This may explain the benefits of some antibiotic guidelines or protocols that do not rely on prescribing single agents or single classes of antibiotics [86].

In addition to potentially preventing antibiotic resistance, combination antimicrobial therapy may be more effective at producing clinical and microbiological responses. This would also help to minimize antibiotic resistance by preventing the horizontal transmission of inadequately treated infections due to antibiotic-resistant pathogens. Trouillet et al. [36] demonstrated that certain antibiotic combinations were more likely to provide higher rates of bacteriologic cure of nosocomial pneumonia among patients admitted to an intensive care unit. Similarly, Bellomo et al. [87] found that, for critically ill patients with a documented infection, the mortality rate among those patients receiving therapy with a single antibiotic was higher than that among those treated with 2 antibiotics, despite similar severity of illness for both groups (35.3% vs. 8.3%, respectively; $P = .049$). In theory, empirical combination antimicrobial treatment could potentially provide coverage for an unsuspected pathogen (e.g., vancomycin for methicillin-resistant *S. aureus*). This treatment could also provide improved coverage for antibiotic-resistant pathogens (e.g., treatment with 2 antipseudomonal antibiotics for suspected infection due to *P. aeruginosa*). Empirical combinations of antimicrobial agents should ideally be based on local patient characteristics and the predominant bacterial flora and their antibiotic susceptibility profiles. The importance of this basis for empirical combinations is highlighted by a recent study demonstrating remarkable variability between institutions in terms of etiologic agents responsible for nosocomial infections [88].

Scheduled antibiotic changes and antibiotic cycling. The concept of scheduled antibiotic changes and antibiotic class cycling has also been advocated as a potential strategy for reducing the emergence of antimicrobial resistance [89]. In theory, a class of antibiotics or a specific antibiotic drug is withdrawn from use for a defined time and reintroduced at a later time in an attempt to limit bacterial resistance to the cycled antimicrobial agents. This type of strategy is a limited method of encouraging heterogeneous use as opposed to homogeneous use of a limited number of antibiotics [90]. Unfortunately, few clinical data are currently available regarding antibiotic class changes or cycling. Several studies, however, have demonstrated that withdrawing an antibiotic or class of antimicrobial agents from use can potentially restore their effectiveness by reducing bacterial resistance to them [33, 91].

Gruson et al. [92] demonstrated a reduction in the incidence of VAP after introducing an antimicrobial program that consisted of supervised antimicrobial rotation combined with restricted use of ceftazidime and ciprofloxacin, both widely prescribed before the institution of the antibiotic program [92]. Each subsequent empirical antimicrobial regimen was based on the predominant identified flora and their antimicrobial susceptibility profiles from the preceding time cycle. The decrease in the incidence of VAP was primarily attributable to a reduction in the number of episodes caused by potentially antibiotic-resistant gram-negative bacteria, including *P. aeruginosa, Burkholderia cepacia, S. maltophilia,* and *A. baumannii.* These findings are similar to those noted by Kollef et al. [93, 94] in an evaluation of scheduled antimicrobial changes for various groups of intensive care unit patients.

More rapid microbiological identification. There is often a delay of hours to days between starting empirical antimicrobial therapy for suspected infection and obtaining the results of clinical cultures. More rapid identification of etiologic pathogens and their antibiotic susceptibility profiles could help reduce the administration of inadequate treatment. Potential future technologies to speed up microbiological identification include molecular techniques, DNA amplification, and use of monoclonal antibodies to bacterial antigens [95–97].

Summary

Inadequate antimicrobial treatment is closely associated with the presence of antibiotic resistance in clinically important pathogens. Clinicians must be aware of the prevailing pathogens that account for community-acquired and nosocomial infections in their hospitals. In addition, the antibiotic susceptibility profiles of these pathogens should be routinely available to physicians to guide their selection of antimicrobial agents. Antibiograms should be updated on a regular basis to report and detect changes in the antimicrobial resistance patterns of these pathogens. Prior antimicrobial administration, which leads to the emergence of and colonization with resistant organisms, is an important risk factor for subsequent administration of inadequate antimicrobial treatment and should be recognized by clinicians prescribing antimicrobial treatment to hospitalized patients. Consideration should be given to the empirical use of an initially broad-spectrum antimicrobial regimen that includes agents not previously administered, especially for coverage of gram-negative bacteria, to minimize the occurrence of inadequate antimicrobial treatment. Such broad-spectrum treatment can usually be narrowed after a relatively short period (i.e., 24–72 h), when the initial culture results become available, without compromising patient outcomes. Future studies of antibiotic practice guidelines and protocols aimed at the reduction of inadequate antimicrobial treatment are needed to assess their potential influence on patient outcomes. Until such data are available, clinicians should at least consider the possibility of

inadequate antimicrobial treatment whenever prescribing antimicrobial agents in the hospital setting.

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