Does Antibiotic Selection Impact Patient Outcome?

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Inadequate antibiotic therapy, generally defined as microbiologically ineffective anti-infective therapy against the causative pathogen, can influence patient outcome. However, the detrimental effects of inadequate antibiotic therapy seem to become weaker in the most severely ill patients with short life expectancies. In addition to severity of illness, other methodological issues should be carefully examined in studies assessing the excess mortality due to inadequate therapy. To adjust for confounding as much as possible in order to obtain an unbiased estimate of the magnitude of the effect of inadequate therapy is a key methodological challenge for future research. With regard to the choice of antibiotic agents, β-lactam and aminoglycoside combination therapy does not seem to improve clinical outcome in most cases of sepsis caused by gram-negative bacteria, including *Pseudomonas aeruginosa* bacteremia. A potential benefit of combination therapy in the treatment of severe pneumococcal sepsis has been suggested in several observational studies, but recently published data have disputed this hypothesis. Finally, better risk scores and laboratory tools are urgently needed to improve the adequacy of empirical antibiotic therapy and patient outcomes.

> *Frapper fort et frapper vite. (Hit hard and fast.)*
> —Paul Ehrlich, address to the 17th International Congress of Medicine, 1913 [1]

Although antibiotic properties of molds and other natural substances had already been described by several scientists at the end of the 19th century, systemically administered antibiotic agents were not introduced into clinical practice until the 1930s. A controlled study published in 1938 showed the survival benefit of sulfonamide therapy, which reduced mortality from 27% (control group) to 8% (treatment group) among patients with lobar pneumonia [2]. Other life-threatening infections responded less robustly, and sulfonamide resistance developed rapidly. In November 1942, penicillin made its first highly acclaimed clinical appearance in the United States, when it was used for treating victims of the Cocoanut Grove fire in Boston, Massachusetts.

The availability of antimicrobial agents has become crucial for modern medicine. Although other public health measures have contributed to increasing life expectancy over the past century, antibiotics have helped to save innumerable lives and to reduce morbidity associated with infections. The success of antibiotics bred their overuse. An increasing prevalence of antibiotic resistance has led to the progressive decrease in the effectiveness of narrow-spectrum agents and to an increase in difficult-to-treat infections. More then ever, selection of the most appropriate antibiotic therapy has become a challenge for clinicians.

Appropriate antibiotic use is commonly defined as the use of an antimicrobial agent that is correct on the basis of all available clinical, pharmacological, and microbiological evidence. It includes narrowing the spectrum when culture and phenotypic results are available, using appropriate dosages and dosing intervals, and respecting additional principles of the judicious prescription of antibiotics [3]. Inadequate antibiotic therapy, generally defined as the microbiological documentation of an infection with a causative pathogen that is not being effectively treated, can influence patient outcome [4]. On the basis of a selection of relevant articles, in the present overview, we discuss

some of the challenges associated with selecting microbiologically adequate therapy, as well as its effect on patient outcome. More specifically, we address the following questions:

1. What is the impact of microbiologically inadequate antibiotic therapy on survival rate and cure rate? What is the magnitude of the benefit associated with the timely use of effective therapy in critically ill patients?

2. What are commonly encountered methodological challenges in observational studies examining the magnitude of this effect? Which methodological issues should be addressed in future research to resolve some important controversies?

3. What constitutes optimal therapy in selected clinical circumstances? In particular, (a) is empirical coverage of certain "low-virulence" pathogens (e.g., *Enterococcus* species and *Candida* species) necessary, and (b) is combination therapy needed for certain types of bacterial infections?

IMPACT OF MICROBIOLOGICALLY INADEQUATE ANTIBIOTIC THERAPY ON SURVIVAL AND CURE RATE

Microbiologically inadequate antimicrobial therapy is an important determinant of outcome in patients with severe infection [4, 5]. A landmark study conducted in the early 1960s demonstrated that microbiologically adequate antimicrobial therapy leads to a case-fatality rate among patients with gram-negative bacteremia that is lower than that among similar patients receiving inadequate therapy [6]. More recently, Garrouste-Orgeas et al. [7] have shown a favorable impact of early adequate antimicrobial therapy on outcome among patients with intensive care unit–acquired bloodstream infection. In that study, in-hospital mortality among patients who received adequate antibiotic therapy >1 day after blood culture sampling (OR, 4.1; 95% CI, 2.2–7.7) was higher than that among patients treated earlier (OR, 2.7; 95% CI, 1.89–4.1). Similarly, other studies have demonstrated that inadequate antimicrobial therapy is an independent risk factor for death among critically ill patients with severe infection [5, 8].

The magnitude of benefit associated with the timely use of effective therapy for critically ill patients may depend on the causative pathogen and population studied. In a study of episodes of *Staphylococcus aureus* bacteremia, Lodise et al. [9] showed that delayed antibiotic therapy (>2 days after positive culture results) was an independent predictor of infection-related mortality (OR, 3.8; 95% CI, 1.3–11). In another study involving critically ill patients with cancer, in-hospital mortality was higher when antibiotic therapy was initiated >2 h after diagnosis (OR, 7.05; 95% CI, 1.17–42.21) [10]. Iregui et al. [11] demonstrated that even microbiologically adequate but initially delayed (>24 h after meeting the diagnostic criteria) antibiotic therapy for ventilator-associated pneumonia was independently associated with higher mortality. These data were

reinforced by the results of a recently published cohort study of patients with septic shock that showed that each hour of delay in antimicrobial administration over the ensuing 6 h after the onset of hypotension was associated with an average decrease in survival of 8% [12].

In contrast, in a large study, Bryan et al. [13] showed that early antibiotic selection for the first 24 h did not influence survival, regardless of the adequacy of the antibiotics selected. However, this latter study showed improved survival among patients receiving adequate antibiotics after the first day of therapy. A lack of association between microbiologically inadequate therapy and increased mortality has been observed by others [14], but this can be explained by (1) the inclusion of patients with non–life-threatening infections (e.g., surgical site infections and community-acquired methicillin-resistant *S. aureus* infection), (2) methodological limitations (e.g., small sample size), or (3) the influence of confounding factors and bias (e.g., inclusion of patients with rapidly fatal disease and a very high severity of illness). For instance, a study investigating the interaction between disease severity and efficacy of antibiotic therapy in 142 critically ill patients with ventilator-associated pneumonia showed that inadequate empirical therapy was associated with a poor prognosis only in patients with moderate severity of illness (table 1) [15]. Conversely, for the group of patients who were most severely ill, neither the adequacy of initial therapy nor the duration of inadequate therapy influenced survival.

Even in the absence of a direct effect on mortality, microbiologically inadequate antibiotic therapy influences the failure rate. This has been shown for a wide range of infections and is often associated with the presence of antibiotic-resistant pathogens. For example, the use of trimethoprim-sulfamethoxazole to treat community-acquired urinary tract infections or pneumonia caused by trimethoprim-sulfamethoxazole–resistant mi-

Table 1. Prognostic factors in patients with ventilator-associated pneumonia, according to multivariate analysis of the interaction between severity of illness and adequacy of early antibiotic therapy.

Prognostic factor	OR (95% CI)
McCabe score	
Nonfatal	1
Fatal	3.4 (1.5–7.6)
LOD score	
≤4	
With adequate AT	1
With inadequate AT	7.2 (1.5–35.5)
>4	
With adequate AT	24.9 (4.8–129)
With inadequate AT	16.5 (2.5–110)

NOTE. Data are from [15]. AT, antibiotic therapy; LOD, logistic organ dysfunction.

croorganisms increases the likelihood of clinical failure (figure 1) [16, 17].

METHODOLOGICAL ISSUES: AN EXAMPLE FROM THE LITERATURE

Important methodological challenges should be considered when interpreting the currently available evidence on the association between microbiologically inadequate antimicrobial therapy and patient outcome. This research question is not amenable to testing in a randomized trial, because it would be unethical to knowingly expose patients to inadequate therapy. Thus, the answer to this question relies on observational studies. Obviously, it is unlikely that inadequate antimicrobial therapy does have some beneficial effect on patient outcome. The key objective of an observational study, then, is to remove as many confounding factors as possible to obtain an unbiased estimate of the magnitude of the effect of inadequate therapy [18].

In one such widely cited study of patients with intensive care unit–acquired bloodstream infection, the crude relative risk (RR) for mortality after microbiologically inadequate therapy, compared with adequate antimicrobial therapy, equaled 2.2, corresponding to a crude OR of 4.1 [19]. By use of a multivariable logistic regression model, an adjusted OR of 6.9 was estimated for the effect that inadequate antimicrobial therapy for bloodstream infection has on in-hospital mortality, after including the use of vasopressors, age, organ dysfunctions, and severity of illness as variables along with inadequate therapy. A major limitation of this analysis was that the factors included in the logistic regression model were only those found to be significantly associated with mortality. A stepwise variable selection approach was used, with a P value of .05 used as the limit for the acceptance or removal of new terms. The problem is that this method does not remove confounding by factors not selected into the model. Many characteristics were identified that distinguished patients receiving microbiologically inadequate antimicrobial therapy from those receiving adequate antimicrobial therapy, such as time spent in the hospital before bloodstream infection and prior use of antimicrobials [19]. Presumably, these factors influenced the probability of inadequate therapy and were also associated with the outcome, although not always to a statistically significant degree. The noninclusion of these variables in the model likely contributed to an overestimation of the effect of inadequate therapy [18, 19].

Observational research on the effect of inadequate therapy is limited by the possibility of residual confounding due to unmeasured variables. The key point is that confounding factors do not have to be statistically significantly associated with the outcome to be confounding factors. Instead of focusing on statistical significance, the analysis should be directed toward a careful consideration of the potential sources of confounding and deriving the least biased estimate of the true causal effect
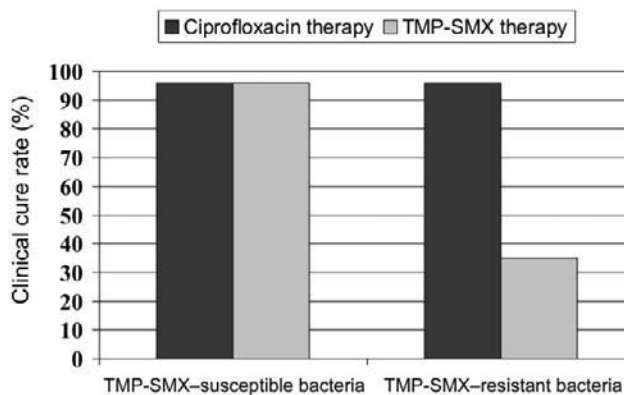

Figure 1. Influence of antibiotic resistance on cure rates for acute uncomplicated pyelonephritis in women: comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (TMP-SMX) (14 days) [17].

[18]. Unfortunately, automated variable-selection methods completely ignore the relationship between the putative confounding factors and the exposure.

One analytic method that has gained widespread application in overcoming problems with confounding is the use of propensity scores. In our context, the propensity score would be the probability (0.0–1.0) of each patient receiving inadequate therapy [5]. After determining the propensity score for each patient by use of the predicted probability of exposure to inadequate antimicrobial therapy, this covariate can then be included along with other confounding variables in the multivariate analysis, which may allow for further adjustment for differences between patients who received or did not receive adequate initial antimicrobial therapy [20].

EMPIRICAL COVERAGE OF SPECIFIC "LOW-VIRULENCE" PATHOGENS

Microorganisms that had traditionally been considered to be of low virulence, such as *Candida* species, *Enterococcus* species, *Acinetobacter baumannii,* and coagulase-negative staphylococci, are an increasingly important cause of nosocomial infections. Therefore, the question arises as to whether antibiotic coverage against these pathogens should be included in the empirical coverage of certain infections.

The clinical significance of enterococci has been the subject of long-lasting debate. In particular, their role as primary pathogens in polymicrobial intra-abdominal infections remains controversial. Although animal models have shown that monomicrobial, intra-abdominal enterococcal infections have limited pathogenicity, several studies have suggested that the presence of enterococci increases the postoperative complication rate and risk of death in certain patient groups [21]. Among patients with monomicrobial enterococcal bacteremia, receipt of effective antimicrobial therapy within 48 h independently predicted

Table 2. Potential mechanisms explaining the suggested benefit of combination therapy for severe, bacteremic pneumococcal pneumonia.

Immunomodulating effect of macrolides
Effect on atypical pathogens in mixed infections
Improved bactericidal effect
Decreased emergence of resistance
Variable protein binding and decreased activity of ceftriaxone
    in severe sepsis

survival [22]. In an extensive literature review [23], we summarized available evidence arguing in favor of using empirical therapy with enterococcal coverage in the following cases: (1) immunocompromised patients with nosocomial peritonitis and severe sepsis who have previously received broad-spectrum antibiotics (e.g., cephalosporins) selecting for *Enterococcus* species, and (2) patients with peritonitis and valvular heart disease or prosthetic intravascular material, which place them at high risk for endocarditis.

Delay in initiating antifungal treatment for critically ill patients may also be associated with worse outcomes [24]. Because no accurate tools for early diagnosis are yet available, many researchers recommend early empirical antifungal therapy for nonneutropenic patients when candidiasis is suspected [25]. Clinical algorithms and risk scores may help to identify the patients at highest risk for candidiasis [25]. There are several options for early empirical and preemptive treatment of candidemia in nonneutropenic patients, including amphotericin B, fluconazole, voriconazole, and echinocandins. A recent study has suggested that voriconazole was as effective as a regimen of amphotericin B followed by fluconazole in the treatment of candidemia in nonneutropenic patients [26]. However, as was outlined in an accompanying editorial [27], the study had several limitations (e.g., relevance of the control group and biased selection of patients) that limit its clinical relevance and generalizability.

Infections with *A. baumannii* are now endemic in many countries. Although generally less virulent than *Pseudomonas aeruginosa*, *A. baumannii* has nonetheless become a problematic pathogen because of increasing resistance to commonly used antimicrobial agents. Because bacteremia due to *A. baumannii* managed with microbiologically inadequate therapy is associated with increased mortality, the intravenous use of polymyxins has reemerged worldwide [28]. Subsequently, physicians are facing the difficult decision of when to institute therapy with polymyxins. At present, clinical evidence does not allow for any firm conclusions about the effectiveness of empirical use of colistin, because the optimal therapeutic regimen for these multidrug-resistant infections remains to be determined.

The increasing use of intravascular catheters contributes to the high incidence of health care–associated infections with coagulase-negative staphylococci (CoNS). In daily practice, it remains a challenge to distinguish clinically significant CoNS from contaminant strains. Because >80% of CoNS are resistant to methicillin, vancomycin appears to be the mainstay of directed treatment for CoNS infections, in addition to removal of infected foreign bodies [29]. Combination therapy, usually by adding rifampicin or gentamicin, seems to be helpful for the treatment of some deep-seated infections with CoNS, mainly prosthetic valve endocarditis. Current guidelines, however, do not recommend specific coverage of CoNS for empirical treatment of severe sepsis.

COMBINATION THERAPY FOR SEPSIS CAUSED BY GRAM-NEGATIVE BACTERIA

As is mentioned above, early adequate therapy reduces mortality associated with gram-negative bacteremia. Nevertheless, there is no consensus regarding the need to use combination as opposed to single-agent antimicrobial therapy to treat these infections. In theory, combination therapy has the following potential advantages: (1) an additive or even synergistic effect in vitro, (2) broader antibacterial coverage for potentially multidrug-resistant microorganisms, and (3) a preventive effect on the emergence of resistance in certain gram-negative bacteria. However, concerns regarding toxicity, costs, and detrimental drug interactions should be considered. In addition, the availability of potent broad-spectrum antimicrobials may render combination therapy unnecessary. Lastly, there are no clinical data showing an undisputable advantage of combination therapy over monotherapy in the treatment of sepsis caused by gram-negative bacteria.

In a systematic review of controlled trials, Paul et al. [30] compared β-lactam monotherapy with β-lactam and aminoglycoside combination therapy in the treatment of gram-neg-
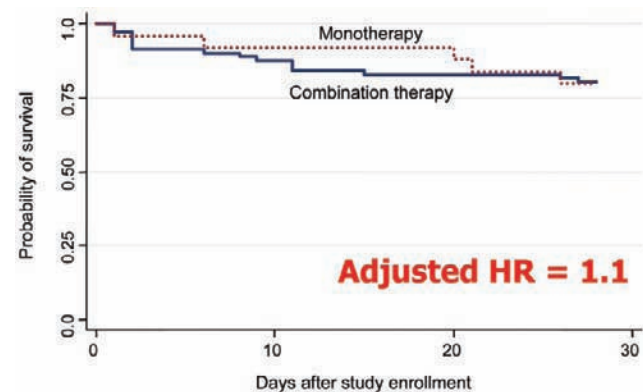

Figure 2. Survival curve for patients with severe pneumococcal sepsis, stratified by receipt of antibiotic monotherapy ($n = 25$) versus combination therapy ($n = 82$) [35]. The risk of death was almost identical after the number of organ dysfunctions and the severity of illness at baseline were adjusted for (adjusted hazard ratio [HR], 1.1; 95% CI, 0.4–3.1; $P = .9$).

Table 3. Issues that should be addressed in future research to resolve important controversies and decrease major deficits in our knowledge of optimal antimicrobial therapy for critically ill patients.

Study type, research topic	Need	Comment
Intervention studies		
Effect of combination therapy on severe pneumococcal pneumonia	Randomized clinical trial	Enrollment requires microbiological test results. Molecular techniques for rapid identification of pneumococcal infection might facilitate patient inclusion.
Clinical effectiveness of rapid microbiological tools to increase the early adequacy of therapy	Randomized clinical trial	Current procedures for approval of PCR-based diagnostic tools do not require randomized studies, despite an urgent need to demonstrate their clinical effectiveness.
Observational studies		
Magnitude of the effect of delayed microbiologically adequate therapy	Accurate multivariate modelling	Use of propensity scores and advanced statistical analyses may generate unbiased effect estimates
Effect of combination therapy on *Pseudomonas aeruginosa* bacteremia	Multicenter, observational cohort studies	Randomised clinical trial unlikely ever to be performed. Pooled analysis of clinical trials investigating new sepsis drugs may provide meaningful observational evidence.
Empirical coverage of "low-virulence" pathogens	Prediction tools and risk score models	Better risk scores are urgently needed to identify patients at high risk of infection with these bacteria

ative bacteremia. Sixty-four trials comprising 7586 subjects were included in the analysis, which showed no significant difference between mortality associated with monotherapy and that associated with combination therapy (RR, 0.90; 95% CI, 0.77–1.06). Moreover, monotherapy tended to be protective against clinical failure (RR, 0.87; 95% CI, 0.78–0.97) and microbiological failure (RR, 0.86; 95% CI, 0.72–1.02). The analysis of subgroups did not show any firm advantage of combination therapy over monotherapy for *P. aeruginosa* infection or for infection with gram-negative versus gram-positive bacteria. Finally, combination therapy did not lower bacterial superinfection rates. Concerning adverse effects, nephrotoxicity was significantly less common with β-lactam monotherapy than with combination therapy (RR, 0.36; 95% CI, 0.28–0.47) [30]. In a similar study, Safdar et al. [31] evaluated the difference between the effects of combination therapy and monotherapy on mortality in patients with gram-negative bacteremia. They included 17 studies, encompassing 3077 subjects. The summary OR was 0.96 (95% CI, 0.70–1.32), indicating that there was no mortality benefit favoring combination therapy [31].

The results of these meta-analyses indicate that combination therapy does not seem to be necessary for the vast majority of patients with sepsis caused by gram-negative bacteria. Importantly, patients receiving an aminoglycoside as a second drug can experience significantly more adverse effects than their counterparts receiving monotherapy with a different class of antibiotics. In practice, uncertainty about the etiologic agent and its resistance profile may justify combination therapy as the initial decision for certain high-risk patients. Indeed, weak evidence argues in favor of a beneficial effect of combination therapy in the case of *P. aeruginosa* bacteremia. In one retro-

spective analysis, the use of adequate combination antimicrobial therapy as empirical therapy until receipt of the antibiogram was associated with better survival than was the use of monotherapy [32]. In the review by Safdar et al. [31], a subanalysis of 5 studies of *P. aeruginosa* infection showed a 50% reduction in mortality among patients treated with combination therapy (OR, 0.50; 95% CI, 0.32–0.79). However, Paul and Leibovici [33] have emphasized the difficulty in concluding from this review that combination therapy is advantageous for the treatment of *P. aeruginosa* bacteremia. Indeed, 4 of the 5 studies in the meta-analysis included single-aminoglycoside therapy in the monotherapy arm. Clearly, with the exception of urinary tract infection, monotherapy with aminoglycosides is not appropriate for treating gram-negative bacteremia.

COMBINATION THERAPY FOR SEVERE PNEUMOCOCCAL SEPSIS

A potential benefit of combination therapy for severe pneumococcal bacteremia and sepsis has been shown in several clinical studies [34], although the exact mechanism of this effect remains unclear (table 2). Several experts already promote combination therapy as the initial option for treating severely ill patients with community-acquired pneumonia who are at high risk for pneumococcal bacteremia. However, recently published data have disputed this view. In a large cohort study, we have not been able to confirm the survival benefit of combination therapy in the case of severe pneumococcal sepsis (figure 2) [35]. Likewise, in another recently published multicenter, observational study, combination therapy did not decrease the failure rate among 638 patients with documented pneumo-

coccal pneumonia [36]. Therefore, other experts are more cautious and underline the urgent need for a controlled trial to provide more-definitive answers [37]. Until these studies are available, combination therapy for bacteremic pneumococcal sepsis should not, in our view, become the standard of care. Antibiotic therapy should be adjusted to active monotherapy as soon as susceptibility results are available. In particular, if *S. pneumoniae* is identified as the sole pathogen, it seems reasonable to discontinue administration of the macrolide.

CONCLUSIONS

In the present article, we have addressed several questions related to the effect and selection of adequate antimicrobial therapy for critically ill patients. Clearly, microbiologically adequate antibiotic therapy for severe infections decreases the excess mortality and failure rate. The detrimental effects of inadequate antibiotic therapy seem to become weaker in nonsevere infections and in infections in the most severely ill patients with short life expectancies [38]. *β*-Lactam and aminoglycoside combination therapy does not seem to improve clinical outcomes in sepsis caused by gram-negative bacteria. Early combination therapy may be advantageous in the case of severe *P. aeruginosa* infection, but more data are required to confirm this assertion. In particular, future studies should clarify whether this possible effect is based on the broadening of therapy to ensure adequate antimicrobial coverage and to prevent the emergence of resistance, rather than on the need for 2 microbiologically agents that are active against *P. aeruginosa.* A potential benefit of combination therapy in the treatment of severe pneumococcal sepsis has also been suggested, but recently published data have disputed this hypothesis. Future studies should attempt to resolve these controversies (table 3).

Because of space constraints, we were not able to cover other important related issues, such as questions regarding whether "broadest-spectrum" empirical regimens (e.g., vancomycin plus imipenem) should not be used for all critically ill patients (i.e., whether and when the gains in effective initial therapy would be offset by the accelerated emergence of resistance) and whether therapy in the intensive care unit should not be optimized according to patient-specific pharmacokinetic and pathogen-specific pharmacodynamic parameters [39].

We have identified several knowledge gaps and methodological limitations in previous studies that should be addressed in future research (table 3). In particular, many studies have not adequately estimated the excess mortality due to inadequate therapy. Removing as much of the confounding as possible so as to obtain an unbiased estimate of the magnitude of the effect of inadequate therapy is a key methodological challenge for future research. Moreover, better risk scores should be developed to distinguish patients at low risk for infection with multidrug-resistant pathogens from those for whom broadest-spec-

trum therapy could be truly beneficial. Rapid microbiological tools are urgently needed to identify drug-resistant pathogens and improve the adequacy of empirical antibiotic therapy and patient outcome. We strongly believe that molecular techniques for the rapid identification of microorganisms and improved markers of severe infections are the most promising candidates to improve antibiotic choice and reduce unnecessary treatment.

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