REVIEW

Appropriate vs. inappropriate antimicrobial therapy

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ABSTRACT

Inappropriate antimicrobial treatment (defined as use of antimicrobial agent to which a pathogen is resistant) or a delay in starting appropriate treatment are both associated with increased morbidity and mortality. Studies of ventilator-associated pneumonia, intra-abdominal infections or bacteraemia document higher mortality in patients who received inappropriate therapy. In addition, the outcome in patients switched from inappropriate to appropriate therapy is better than for patients who remained on inappropriate therapy, but the benefit is not as great as for those who were started on appropriate therapy initially. While inappropriate therapy undoubtedly has an important influence on outcomes, it needs to be considered in the context of other patient risk-factors, such as co-morbid conditions, severity score measures, and functional status. When assessing the impact of inappropriate therapy on outcomes such as length of hospital stay, it is important to be as precise as possible about the time of onset of infection. Failure to do so may lead to inaccurate estimation of the effect of inappropriate therapy. While the likelihood that resistant pathogens can increase costs throughout the healthcare system is generally recognised, an under-appreciated aspect of resistance is its consequences for patients and their carers. Initiatives are underway to gauge the impact of resistance and strategies to combat its spread.

Keywords Antibacterial agents, cost, nosocomial infection, outcome assessment, review, ventilator-associated pneumonia

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INTRODUCTION

The dictionary definition of 'appropriate' is 'suitable or right for a particular situation or occasion'. Therefore, inappropriate treatment encompasses the wrong choice of antibiotic or use of an agent to which the pathogen is resistant. This definition therefore includes excessive treatment in addition to inadequate treatment. Inappropriate antimicrobial therapy is associated with increased mortality in bacteraemia, peritonitis, and ventilator-associated pneumonia (VAP). In addition, it has consequences for the healthcare system and effects on patients, and their carers and families. This review will focus on the wide-ranging impact of one type of inappropriate therapy, namely use of an agent to which the pathogen is resistant, and the effects of delays in initiating appropriate treatment.

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IMPACT OF INAPPROPRIATE TREATMENT

Evaluating the consequences of inappropriate treatment in a randomised, double-blind trial would be unethical. However, observational studies do allow insight into its impact. One such study was conducted by Luna *et al.* [1], who compared two treatment approaches in 132 patients exhibiting symptoms of VAP. In one approach, antimicrobials were administered only after the diagnosis of pneumonia had been confirmed microbiologically by bronchoscopy with bronchoalveolar lavage (BAL). In the second approach, empirical antimicrobial treatment was given as soon as a clinical diagnosis of VAP was made. The study examined the adequacy of coverage at three time-points: prior to BAL; post-BAL, or when culture results were available. The results revealed that when antimicrobial therapy was initiated before BAL, the mortality

rate was lower when the drug matched the pathogen (i.e., appropriate therapy) than when the drug did not match the pathogen (i.e., inappropriate therapy). If treatment with an appropriate drug was delayed until post-BAL or until culture results were available, mortality rates were higher in both of these groups than in the group that received appropriate treatment from the beginning. These results show that timely administration of appropriate antimicrobial treatment can improve survival in patients with VAP. Moreover, while patients in the study who were switched to appropriate antibiotics after culture results were available did better than patients who remained on inappropriate therapy, the outcome was not as good as for those who started on appropriate antibiotics from the beginning.

The benefit of early, appropriate treatment is also illustrated by Mosdell *et al.* [2], who conducted a retrospective chart review of 480 patients with secondary bacterial peritonitis. In that study, outcomes were compared for patients who received appropriate therapy based on culture data from samples obtained intra-operatively and patients who received inappropriate therapy. Patients who received empirical treatment with an appropriate antimicrobial agent at the time of surgery had fewer wound infections (14.4% vs. 26.5%), abscesses (10.5% vs. 34.7%), re-operations (13.9% vs. 36.7%), and other complications (18.9% vs. 51.0%), as well as lower mortality (5.6% vs. 12.2%), than those who received an empirical antimicrobial agent with inadequate coverage. This study is important not only because it highlights the importance of appropriate therapy in improving outcomes, but also because it shows that appropriate treatment is only one of many factors that influence outcomes. In this study, about one patient in five developed complications despite appropriate antibiotic administration, and half the patients got better even though they received an inappropriate antibiotic.

Although neither of these studies by Luna *et al.* or Mosdell *et al.* was a prospective randomised trial, both suggest that the timing of antimicrobial treatment is important. Treating only after the microbiological test results are obtained ensures that the correct antimicrobial is chosen, but this strategy increases the risk of a worse outcome due to delayed treatment. Changing to the right antibiotic once the culture results come back is not as beneficial as getting the antibiotic right from the start, possibly because of physiological deterioration of the patient or because of bacterial dissemination or abscesses, which are difficult to treat with antibiotics.

In a prospective cohort study of 492 critically ill patients [3] admitted to the intensive care unit (ICU) with a bloodstream infection, inadequate antimicrobial treatment proved to be the most important risk-factor for in-hospital mortality. In this study, inappropriate treatment was defined as: the microbiological documentation of infection, such as a positive blood culture result, that was not effectively treated at the time when the causative pathogen was known; or the absence of antimicrobial therapy directed at a likely class of microorganisms (e.g., absence of therapy for *Candida*); or the administration of an antimicrobial to which the pathogen responsible for the infection was resistant (e.g., empirical treatment with oxacillin for bacteraemia subsequently attributed to methicillin-resistant *Staphylococcus aureus* (MRSA) on the basis of blood culture results). The mortality rate for patients who initially received inappropriate antimicrobial treatment (61.9%) was significantly greater than the rate for patients who received antimicrobial treatment that matched the pathogen from the start (28.4%; $p < 0.001$).

In addition to illustrating the impact of inappropriate treatment on mortality rates, this study also provides useful information on hospital mortality rates according to causative pathogen (Fig. 1) [3]. The hospital mortality rate showed a

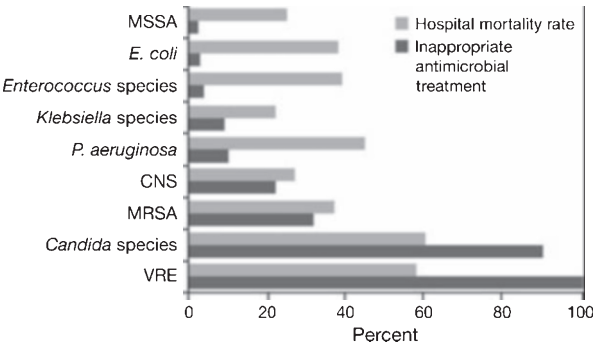

Fig. 1. Inappropriate antimicrobial treatment and mortality rates with common bloodstream infection pathogens. Reproduced with permission from Ibrahim *et al.* [3]. CNS, coagulase-negative staphylococci; MRSA, methicillin-sensitive *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*; VRE, vancomycin-resistant enterococci; *E. coli*, *Escherichia coli*; *P. aeruginosa*, *Pseudomonas aeruginosa*.

statistically significant relationship to the rate of inappropriate treatment for individual micro-organisms (Spearman correlation coefficient = 0.8287; p 0.006). However, despite low rates of inappropriate treatment for methicillin-sensitive *S. aureus* (MSSA) infection or *Escherichia coli* infection, the mortality associated with these infections was nearly as high as that for infections due to resistant organisms. This further indicates that inappropriate therapy is not the only factor determining mortality. Factors such as patient status and pre-morbid conditions also affect patient outcome.

Lodise *et al.* [4] studied the effect of delayed appropriate treatment on clinical outcomes in patients with *S. aureus* bacteraemia who had differing levels of risk-factors. They first identified the breakpoint for infection-related mortality according to the time from when patients received antimicrobial therapy (Fig. 2). The time breakpoint that maximised the difference in infection-related mortality overall was 44.75 h, which served to define treatment given <44.75 h after *S. aureus* identification as early treatment, and treatment after 44.75 h as delayed treatment. Infection-related mortality for the early-treatment group was 19.3% and that for the delayed-treatment group was 33.3% (p 0.05).

To evaluate the importance of other patient risk-factors for outcomes, the investigators assessed whether the impact of delaying treatment was the same for severely ill as for lower-risk patients. They used the Acute Physiology and Chronic Health Evaluations (APACHE II) scoring method to measure risk. An APACHE II score ≥15.5 maximised the difference in the infection-related mortality, providing a dividing point between high-risk and low-risk patients (Fig. 2). The group with an APACHE II score <15.5 had the lowest risk of mortality (6.7%), and no significant difference in outcomes was observed between delayed treatment (3.8%) and early treatment (7.8%). In the group with an APACHE II score ≥15.5 and high-risk sources of infection (e.g., osteoarticular infection, skin and soft-tissue infection, or pressure ulcer), the mortality rate was very high (56.6%), and was significantly higher in the delayed-treatment group than in the early-treatment group (86.7% vs. 44.7%, respectively). In patients with an APACHE II score ≥15.5 but no high-risk sources of infection, the mortality rate was high (12.5%) and the difference between delayed treatment (28.6% mortality) and early treatment (5.9% mortality) was marked. Therefore, it is important to relate the consequences of delayed treatment to individual patients and their risk-factors.

Leibovici *et al.* [5] have also analysed the risk-factors for mortality. In this study, inappropriate treatment was one of several risk-factors associated with increased likelihood of death in a logistic regression model. The odds ratio for fatality in a patient given inappropriate treatment was 1.6, and the effect was independent of other risk-factors, which included older age, congestive heart failure, corticosteroid treatment, prior antibiotic treatment, endotracheal intubation, neutropenia, and septic shock (Fig. 3). Thus, it is crucial to consider the inappropriate or delayed antibiotic therapy in the context of these other risk-factors.

As described above, inappropriate therapy is associated with negative outcomes in terms of mortality. It is difficult to determine the prevalence of inappropriate therapy, as the rates

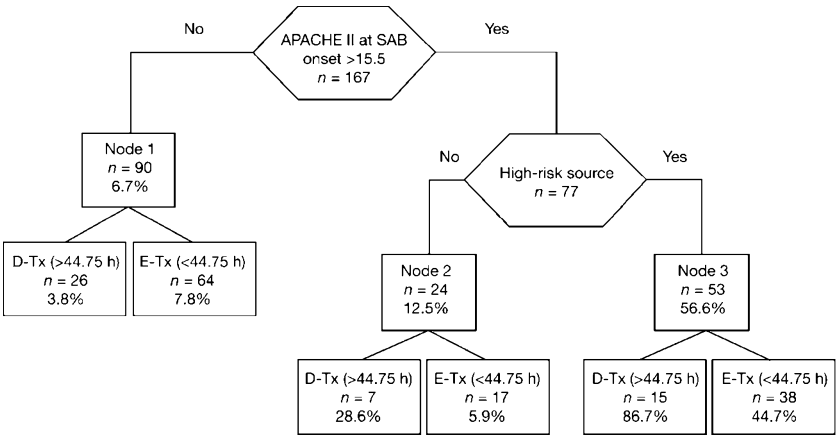

Fig. 2. Classification and regression tree (CART) analysis of predictors of infection-related mortality in *Staphylococcus aureus* bacteraemia. Reproduced with permission from Lodise *et al.* [4]. APACHE II, acute physiology and chronic health evaluation; D-Tx, delayed treatment; E-Tx, early treatment; SAB, *S. aureus* bacteraemia.

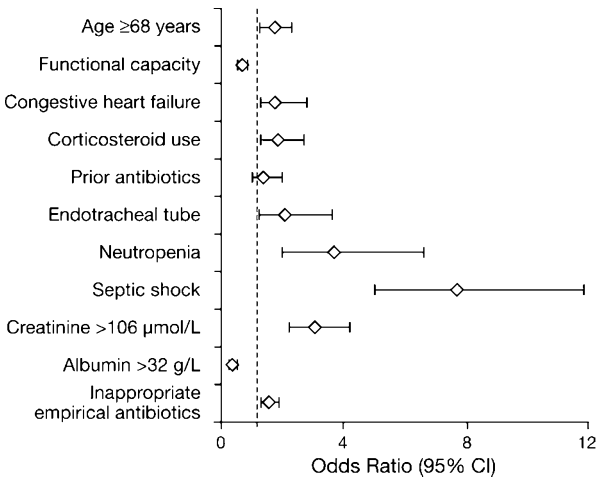

Fig. 3. Odds ratio of fatality related to inappropriate empiricaltreatment and other demographic, physiological and microbiological risk-factors [5].

reported in the literature vary widely among studies [3,4,6,7] (Table 1). Nevertheless, on the basis of these studies, it appears to be common.

Given the significant consequences of inappropriate therapy and its prevalence, efforts should be made to ensure that appropriate antibiotic therapy is undertaken in order to improve outcomes. An approach that may guide therapy is the use of computerised decision-support systems. These are being developed to direct the physician in antimicrobial choice and timing; TREAT is one such system that has been evaluated in a clinical setting [8]. It is a based on a causal probabilistic network, where known causal relationships between the risk-factors put into the system and the magnitude of their outcomes are used to determine therapeutic recommendations. In a study with a cluster randomised trial design, hospital wards that used TREAT prescribed appropriate empirical treatment significantly more frequently than wards that did not. This was despite the fact that only half of the physicians in the intervention arm used the support system. Wards using the system had statistically significant reductions in antimicrobial costs [8]. Mortality and length-of-stay outcomes were lower in wards using TREAT than in those not using it, but the difference was not statistically significant (Table 2). Therefore, tools such as TREAT hold promise because they could become a useful guide to the physician and may eventually help increase the rate of appropriate empirical treatment and improve outcomes. The TREAT system has been

Table 1. Inappropriate antimicrobial treatment of patients in the hospital [1,3,4,6,7]

Author	Study year	Population type	Study type	Setting	Total *N*	Inappropriate treatment (%)
Ibrahim *et al.* 2000 [1]	1997–1999	Bloodstream infections	Prospective cohort	ICU admissions	492	29.9
		Sub-population: CA-BSI			193	19[b]
		Sub-population: HA-BSI			291	35[b]
		Sub-population: (CA + HA)-BSI			8	75[b]
Lodise *et al.* 2003 [3]	1999–2001	Bacteraemia	Retrospective cohort	Detroit receiving	167	28.7
Luna and Vujacich 1997 [4]	1992–1995	NP/VAP	Prospective	ICU (Argentina)	50[a]	68
Das and Jumaa. 2007 [6]	2001–2002	Bacteraemia	Prospective	Selly Oak Hospital (UK)	140	15
Heyland *et al.* 1999 [7]	Not available	VAP	Prospective, matched cohort	Canada	142	21.8

BSI, bloodstream infection; CA, community-acquired; HA, hospital-acquired; ICU, intensive care unit; NP, nosocomial pneumonia; VAP, ventilator-associated pneumonia.
[a]Total *N* = 132; bronchoalveolar lavage (BAL)-negative = 67 patients; BAL-positive = 65 patients, of whom 50 had antibiotic treatment prior to BAL procedure (early antibiotic) and 15 had antibiotic treatment post-procedure.
[b]Estimated.

Table 2. TREAT decision support system [8]

Outcome	Intervention	Control	Odds ratio	p value
Appropriate antibiotics (ITT)	72.7%	64.5%	1.48 (CI 1.03–2.11)	0.033
Appropriate antibiotics (per protocol[a])	85.1%	64.5%	3.42 (CI 1.97–5.96)	0.001
Mean total antibiotic cost	€565	€623		0.007
Mean LOS	8.83 days	9.45 days		0.055
Mortality (ITT)	12.9%	14.3%	0.93 (CI 0.73–1.19)	NS
Mortality (per protocol)	9.7%	11.9%	0.90 (CI 0.58–1.39)	NS

ITT, intention to treat; LOS, length of stay; NS, not significant.
[a]Per-protocol analysis was performed including patients in intervention wards for whom physicians prescribed one of the antibiotics from the three top-ranking treatments suggested by TREAT.

made available as a commercial product, but it is unlikely that hospitals will be prepared to make the necessary financial and time commitments without further evidence of cost-effectiveness.

INAPPROPRIATE TREATMENT AND RESISTANCE-RELATED COSTS

Inappropriate antimicrobial treatment has negative effects beyond increased rates of mortality and morbidity. Treatment failures can require extra hospital days, additional laboratory costs, and costly isolation and other infection control measures [9], and may affect subsequent empirical antibiotic choices, resulting in higher drug costs. Additional costs also stem from the need to develop new antimicrobial agents and to implement educational programmes on antimicrobial resistance [10].

The increase in costs that accompany the detection of resistant organisms is illustrated by an outbreak of infection with penicillin-resistant *Streptococcus pneumoniae* in a hospital for the elderly. Ten cases of penicillin-resistant *S. pneumoniae* were detected, and this led to a change in antibiotic policy. The mean monthly antibiotic cost for the period preceding the detection of the resistant strain was approximately £2900 (cost in 1994). This more than doubled to about £7400 in the month when the resistant strain was detected, reflecting the fact that penicillin was largely replaced by cefotaxime as a precaution to stem the emergence of further resistant cases [11]. The costs fell over subsequent months but remained higher than before the resistant pathogens were detected.

To evaluate outcomes, reliable and accurate data are necessary. The data should be collected so as to take the time-dependency of the event that leads to the outcome into account. A study by Blot *et al.*[12] that assessed mortality rates in patients with bacteraemia involving MRSA and MSSA illustrates the importance of considering the time to an event. The attributable mortality rate for MRSA was approximately 22% higher than that for MSSA. However, mortality rates did not differ in the first few weeks of ICU stay, and the difference was only apparent after 35 days. Once patients developed MRSA bacteraemia (20 days vs. 8 days for MSSA bacteraemia), the differences in outcome became greater with increasing ICU and hospital stay.

Mathematical models are being developed that incorporate time-dependent variables. One such model, called ChangeLOS [13], is being developed to account for timing of events when determining the effect of a complication on length of stay (LOS). It allows multistate systems to be described and can determine the probabilities of transition between these states. In turn, this allows the timing of events to be incorporated into outcomes analysis.

The ChangeLOS model has been applied to assess the extent to which nosocomial pneumonia affects LOS. Using data from an 18-month cohort in five ICUs, the model computed that nosocomial pneumonia prolongs LOS by an average of 6.2 days [14]. In contrast, a traditional matched analysis of the data (i.e., comparison between infected and non-infected patients) overestimated the effect of nosocomial infection by a factor of more than two. This is because matched analysis incorrectly treats nosocomial infection as a baseline covariant, whereas it needs to be considered as a time-dependent variable. Therefore, accurately defining the relationship between an event (e.g., infection) and an outcome (e.g., death or LOS) requires systematic patient follow-up and

frequent collection of data on the occurrence of the events of interest.

Another application of mathematical modelling is demonstrated by the work of Lipsitch *et al.* [15]. They developed a multistate model of bacterial transmission within a hospital that can be used to study the effects of measures to control nosocomial transmission and reduce antimicrobial resistance. In the model, subjects can move from one state to another (e.g., infection with a susceptible pathogen or no infection). The fact that patients can move from one state to another, both in the model and in real life, highlights the need to follow patients and determine the time when events of interest, such as acquiring a resistant organism, occur.

INCREASING PATIENT AWARENESS

Appropriate antimicrobial treatment is no longer a topic discussed only among infectious disease specialists. Hospital-acquired infections and antibiotic resistance are frequently in the news, and the public is becoming informed. An initiative to increase patient awareness of healthcare-associated infections has been launched in the UK by the National Concern for Healthcare Infections (http://www.nc-hi.com). It began by providing updated information on MRSA and expanded to cover other resistant pathogens relevant to hospital-acquired infections. The service now includes a newsletter and information on measures that a patient can take to reduce the risk of acquiring an infection in the hospital setting. The service also collects and disseminates stories from patients who recount their experiences and their interaction with the hospital after a serious infection. Patient stories are a very powerful way to influence policy-makers and health service providers to take action to improve patient safety. Examples can be found on the WHO's Patients for Patient Safety site at http://www.who.int/patientsafety/patients_for_patient/who_we_are/en/index.html.

The societal dimension of resistance is one aspect of the BURDEN of Resistance and Disease in European Nations project. The aim of this initiative is to generate awareness and understanding among policy-makers and communities at large to enable action to be taken on the emergence and spread of antimicrobial resistance. It will provide valid and comparable information on the burden of disease and the costs attributable to infections caused by antimicrobial-resistant pathogens in European Union countries. As part of the project, a descriptive study will be carried out on experiences with, and outcomes of, infections caused by antimicrobial-resistant pathogens, incorporating information from patients and carers. Another European project is Mastering Hospital Antimicrobial Resistance (MOSAR). It is examining factors determining the spread of nosocomial pathogens in healthcare facilities and in high-risk settings. It will also explore the efficacy and economic impact of control strategies. It is anticipated that the resulting knowledge will be disseminated to, and translated into, improved patient care by carers and health policy-makers.

CONCLUSION

Inappropriate treatment (i.e., using an agent to which the pathogen is resistant) and delays in effective treatment increase rates of morbidity and mortality. Changing from inappropriate to appropriate treatment once culture results have become available can improve outcomes but not to the same extent as initial appropriate antimicrobial treatment. Appreciation of patient risk is important, as the likelihood of a poor outcome with delayed appropriate therapy appears to be greatest among critically ill patients, especially those with high-risk sources of infection. Despite the undoubted importance of inappropriate therapy, it is but one of many factors that influence clinical outcome, and should be considered in the context of these other factors.

The economic impact of inappropriate therapy extends beyond the costs attributable to morbidity and mortality. Costs to a healthcare system include those due to implementing isolation procedures, changes to laboratory testing, and education to improve infection control and antimicrobial management. In evaluating the consequences of inappropriate therapy, models should consider infection as a time-dependent variable, as failure to do so can lead to an inaccurate estimate of the associated effects. The impact of inappropriate therapy is likely to be better understood with the development of models that incorporate the time-dependency of events.

The consequences of antimicrobial resistance can be particularly devastating for patients, their

carers, and their families. Initiatives to increase awareness of infection with resistant organisms are underway in Europe. It is hoped that these will help to better gauge the effects of antimicrobial resistance and identify strategies to better tackle it.

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