Clinical implications of antimicrobial resistance for therapy

Alasdair P. MacGowan1,2* on behalf of the BSAC Working Parties on Resistance Surveillance

1Bristol Centre for Antimicrobial Research and Evaluation, North Bristol NHS Trust, Bristol, UK; 2Department of Medical Microbiology, University of Bristol, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, UK

The last decade has seen a significant improvement in published evidence to show the clinical predictive value of phenotypic susceptibility testing with categorization of pathogens as ‘susceptible’ or ‘resistant’ based on clinical breakpoints. Most of the published data are based on retrospective or prospective observational clinical studies of patients treated with appropriate [pathogen(s)-susceptible] or inappropriate [pathogen(s)-resistant] chemotherapy. Appropriate therapy has been shown to improve outcomes in infections occurring in hospitals, such as bloodstream infection (BSI) and pneumonia in the intensive care unit. Infections due to specific pathogens such as extended-spectrum β-lactamase-producing Enterobacteriaceae, Pseudomonas aeruginosa and Staphylococcus aureus also respond better to appropriate than inappropriate antibiotics. The situation with vancomycin-resistant enterococci is less clear, perhaps due to the increased importance of patient confounders. Streptococcus pneumoniae when causing acute pneumonia with or without BSI is a well-known exception to the predictive value of laboratory-defined resistance. Antibiotic resistance also impacts on outcomes in the community where the evidence is best for urinary tract infection. The clinical studies are compatible with the current pharmacokinetic/pharmacodynamic paradigm used to explain and predict antibacterial effects and therefore have a sound basis in antimicrobial science. These data underline the importance of well-constructed epidemiological studies to determine the prevalence of antimicrobial resistance in clinical practice and the central place of laboratory-based susceptibility testing in dictating antimicrobial therapy and so optimizing patient outcomes.

Keywords: clinical outcomes, bacteraemia, hospital infection

Introduction

Antimicrobial resistance in pathogenic bacteria can be defined in two ways: first with reference to the normal population of bacteria that exist before exposure to the antimicrobial agent and secondly in terms of adverse clinical outcomes related to uncontrolled infection if a patient receives that antimicrobial. These two concepts are encompassed in the European Committee on Antimicrobial Susceptibility Testing (EUCAST) definitions of resistance. Microbiological resistance or non-wild-type resistance is defined by the presence of an acquired or mutational resistance mechanism to the drug in question. A bacterial isolate can be categorized as microbiologically resistant (non-wild-type) by applying an appropriate cut-off in a defined phenotypic test system (for example, an MIC determination). These cut-offs will not change with changing clinical circumstances. In contrast, clinical resistance is defined by a level of antimicrobial activity associated with a high likelihood of therapeutic failure. Again, an organism can be categorized as clinically resistant using a cut-off value in a phenotypic test system (for example, an MIC or zone size determination). Clinical breakpoints to define resistance evolve over time as more information becomes available on the clinical impact of resistance mechanisms and as drug dose and modes of administration change. Implicit in the definition of clinical resistance is the concept that exposing a potential pathogen to a drug to which it is susceptible will produce an improved outcome compared with therapy with a drug to which the pathogen is resistant. The size of the benefit may be subject to debate: for example, is a small benefit to a large number of patients equivalent to a large benefit to a small group of those who receive the drug? For ethical and moral reasons, it is impossible to knowingly treat patients with antimicrobials to which their infecting pathogen is resistant, hence prospective randomized controlled studies have not been conducted to address the issue of the significance of clinical resistance. However, in clinical practice, a minority of patients receive antimicrobials to which the pathogen causing infection is resistant. This allows the use of either retrospective or prospective observational studies of cohort or case-matched designs to be employed to study the clinical impact of resistance tested by MIC or any other phenotypic system (for example, zone diameter, or in an automated susceptibility testing system).

*Corresponding author. Tel: +44-117-959-5651/2; Fax: +44-117-959-3154; E-mail: alasdair.macgowan@nbt.nhs.uk
Such studies are not without methodological problems. These factors become even more critical when studies attempt to address the timing of appropriate therapy: for example, must therapy start immediately the patient manifests infection or is some delay acceptable? In addition, if the magnitude of the benefit of appropriate therapy is to be assessed accurately, then the pathogens treated and the patient population will have a significant impact on the conclusions. The pathogens involved in studies of bloodstream infection (BSI) are pivotal; for example, the isolation of a coagulase-negative Staphylococcus may only require central line removal and no antimicrobial therapy, whereas for other lower pathogenicity isolates such as vancomycin-resistant Enterococcus, the role of appropriate therapy may be difficult to assess, because patients’ factors may dominate all other risk factors for poor outcome. The patient population studied is also important, as well as the size of the group studied: clearly, a small sample size may be associated with missing an important effect. Confounding patient factors have to be corrected for, and those patients with rapidly fatal disease are excluded from the analysis. Despite these methodological concerns, there are a large number of publications comparing appropriate with inappropriate chemotherapy and reporting outcomes, mainly mortality. A smaller number of publications have attempted to quantify how timing of appropriate chemotherapy impacts on outcome, although this may also be affected by patient factors. For example, the time allowable to give appropriate chemotherapy in the presence of septic shock is very short, but is longer in many patients with methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia.

In the following sections, the importance of clinical resistance for therapeutic outcomes in a range of clinical situations will be addressed and will be followed by a discussion on its impact for specific infections, due to S. aureus, extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, Pseudomonas aeruginosa, vancomycin-resistant Enterococcus spp. and Streptococcus pneumoniae. In the following sections, I will assess the importance of clinical resistance for therapeutic outcomes in a range of clinical situations: BSI/pneumonia in intensive care unit (ICU) and urinary tract infection (UTI) in the community. Then I will report on its impact.

**BSI**

There are a number of clinical studies that suggest that appropriate antimicrobial chemotherapy has a beneficial effect on patients’ outcomes in BSI. In contrast, some studies of BSI in the ICU or in adult patients with cancer have not been able to associate inappropriate antibiotics (empirical or not) with mortality. In patients with bacteraemia due to Gram-negative bacilli, the use of appropriate antibiotics reduced deaths by about half, independent of severity of infection, including shocked patients. Not all studies have reported on the timing of appropriate chemotherapy. Some have defined it from the availability of microbiological data. Early appropriate therapy was also protective of circulatory shock, reducing its risk by half. In a prospective observational study of BSI in a teaching hospital, appropriate antibiotic therapy reduced mortality and patients’ length of stay, again even in the presence of shock. The biggest benefit of appropriate therapy was in paediatric patients, intra-abdominal infection, skin and skin structure infections and BSI due to Klebsiella pneumoniae and S. pneumoniae.

A similar retrospective study of BSI in medical patients (mainly those with haematological malignancy, AIDS and others) indicated a halving of mortality in those who received appropriate therapy. Timing of appropriate therapy appeared important in haematological malignancy as early appropriate therapy (within 48 h) reduced mortality. This was not true of other patient groups. A retrospective study of BSI in the ICU indicated that appropriate antibiotic therapy improved outcomes, and a prospective cohort study performed in a mixed medical/surgical ICU in a teaching hospital confirmed these findings. More recently, in a prospective matched study of patients with sepsis in ICU, inadequate empirical antimicrobial therapy was associated with excess mortality and length of stay.

**Pneumonia in ICUs**

There are a number of prospective and retrospective studies of pneumonia in the ICU, including ventilator-associated pneumonia (VAP), indicating that appropriate empirical antibiotic therapy reduces mortality by about half. Of the studies in VAP, one addressed the relationship between baseline severity of disease, inappropriate empirical therapy and outcome. In patients with more-severe disease, inappropriate empirical therapy increased mortality, but not in all patients. The risk of inadequate empirical therapy has been related to the presence of multidrug-resistant bacterial infection, polymicrobial infection and late-onset VAP occurring after 5 or more days in ICU.

**Other clinical situations in hospitalized patients**

A number of studies have assessed the importance of appropriate empirical therapy in community-acquired intra-abdominal sepsis, mainly secondary peritonitis. Patients who receive antibiotics not covering all the bacteria initially isolated or both aerobes and anaerobes are less likely to have a successful clinical outcome and also have an increased length of hospital stay.

A similar situation applies in patients with severe illness requiring ICU admission, although the timing of appropriate therapy was not addressed. A prospective cohort study indicated that prior antimicrobials, BSI, increasing APACHE II score and decreasing age were associated with increased risk of inappropriate antibiotic therapy. Overall mortality and infection-related mortality were higher in patients treated with inappropriate antibiotics.

In a large study of monoclonal anti-tumour necrosis factor antibody (MONARCS), 2364 patients with suspected sepsis were enrolled. Although 91% of the patients received adequate early empirical antibiotic therapy, the mortality rate was 33% in those who received adequate treatment versus 43% in those who did not (P < 0.001). It seems clear therefore that adequate early antibiotic therapy reduces mortality in patients with suspected sepsis.

**Infections treated in the community**

A number of studies have addressed the impact of antibiotic resistance on infection outcome in community practice. All but one of these studied UTI.
Outcomes of therapy

In a randomized controlled trial (RCT) of two fluoroquinolones versus co-trimoxazole, it was noted that co-trimoxazole-resistant isolates were associated with lower rates of bacteriological eradication and higher rates of clinical failure than susceptible strains. Similar observations were made during an RCT of ciprofloxacin versus co-trimoxazole for acute uncomplicated pyelonephritis. Patients infected with co-trimoxazole-resistant bacteria, mainly *Escherichia coli*, had significantly higher rates of clinical and bacteriological failure.

In a study designed specifically to assess the clinical impact of co-trimoxazole resistance in uncomplicated UTI in women, Raz et al. showed that clinical and microbiological cures, as defined by the absence of bacteraemia, were significantly worse with resistant organisms at 5–9 and 28–42 days after stopping therapy.

Another study of uncomplicated UTI in women treated with trimethoprim found that trimethoprim resistance resulted in longer time to symptom resolution, greater reconsultation rates, more subsequent antibiotics and higher rates of bacteriuria at 1 month compared with the treatment of susceptible strains.

A single retrospective time-series analysis of antibacterial treatment of MRSA-associated skin and skin structure infections with appropriate chemotherapy (co-trimoxazole) demonstrated speedy symptom resolution (see section on *S. aureus*).

**Enterobacteriaceae**

*Extended-spectrum β-lactamases*

Infections caused by *E. coli*, *Klebsiella* spp. and *Proteus mirabilis* are associated with adverse clinical outcomes when treated with cephalosporins (cefuroxime, cefotaxime, ceftriaxone, cefazidime or cefepime).

Patients infected with ESBL producers have longer delays before they receive appropriate antibacterials, a longer duration of hospital stay, cost more to treat, are less likely to have favourable clinical and microbiological outcomes and have a higher mortality than matched control patients. It is also clear that the risk of clinical failure of therapy with cephalosporins is related to the cephalosporin MIC rather than the presence of the ESBL enzyme itself. This is in keeping with non-clinical pharmacodynamic models used to evaluate the therapy of these infections. In man, ≤33% of the patients (*n* = 14) failed therapy if the MIC for an ESBL producer was ≤2 mg/L; this compared with ≥67% patients failing therapy when the MIC was ≥4 mg/L. A similar impact of MIC has been reported with cefepime.

The outcome of treatment of ESBL producers from non-urinary sites with piperacillin/tazobactam is probably also related to the MIC of the pathogen rather than just the presence of an ESBL. Similar clinical results were reported in treating ESBL-producing *K. pneumoniae* in neonates with imipenem or piperacillin/tazobactam. All the infections were due to isolates susceptible to piperacillin/tazobactam using CLSI methods (MIC ≤ 16 mg/L). Others have reported less-favourable outcomes, for example, in a retrospective case review of 21 patients with infection due to ESBL-producing *E. coli* or *Klebsiella* spp., of which 35% to 50% were susceptible to piperacillin/tazobactam, and the clinical response was 50% to 55% compared with 100% cures with carbapenems. In a more recent study, clinical success was reported in 10/11 infections in non-urine sites when the piperacillin/tazobactam MICs were ≤16 mg/L, but 2/6 infections responded if MICs were >16 mg/L. In urine infections, piperacillin/tazobactam was 100% (*n* = 6) clinically successful, irrespective of MIC, presumably due to the high urinary concentrations achieved.

Therapy with carbapenems or fluoroquinolones if the ESBL-producing strain is susceptible has generally been associated with the best clinical outcomes. Accepting that appropriate chemotherapy has a favourable impact on outcomes with ESBL producers, controversy remains as to the timing of therapy. In a retrospective case series (in which the administration of a broad-spectrum cephalosporin as definitive therapy for ESBL bacteraemia was associated with increased mortality), the use of appropriate or inappropriate empirical therapy had no impact on outcome provided that therapy was adjusted once susceptibility results were known. In contrast, another retrospective cohort analysis of bacteraemia caused by ESBL-producing Enterobacteriaceae identified inadequate initial therapy as impacting adversely on outcome. In this study, adequate therapy is defined as the period from the time the first positive blood culture was obtained and up to 72 h thereafter. Clearly, more studies are required to understand the timing of appropriate chemotherapy and the possible impact of the severity of patient illness at presentation.

**Other studies on Enterobacteriaceae**

A number of other studies have looked at the impact of appropriate antimicrobial therapy in BSI due to Gram-negative rods (*E. coli*, *Enterobacter* spp., *K. pneumoniae*, *P. aeruginosa* and *Acinetobacter* spp.). These show similar findings in that multidrug-resistant pathogens (*E. coli* or *Acinetobacter* spp.) were associated with an increased risk of inappropriate initial antimicrobial chemotherapy, and this was related to the increased mortality observed in these patients. However, such patients often also have more co-morbidities. Resistance to cephalosporins due to the hyperproduction of an inducible AmpC enzyme in *Enterobacter* spp. during antibiotic therapy has been associated with longer hospital stays, higher costs and increased mortality after adjustment for other risk factors. Interestingly, despite being associated with increased risk of multiresistance in Gram-negative rods from bacteraemic patients, the presence of integrons did not affect 14 day mortality in a prospective study.

*P. aeruginosa*

Inappropriate definitive antimicrobial therapy has been related to mortality in patients with *P. aeruginosa* bacteraemia, including cancer patients, but excluding infections related to intravenous lines. Clinical outcomes in bacteraemia have also been linked with pharmacodynamic optimization of fluoroquinolone and aminoglycoside therapy (target C\(_{\text{max}}\)/MIC > 8). In contrast, the role of appropriate initial antibiotic therapy is less clear. Miek et al. performed a retrospective analysis of *P. aeruginosa* bacteraemia, showing that inappropriate initial therapy was an independent risk factor for subsequent death. In addition, Bodey et al. showed that a delay in appropriate therapy of 1–2 days in cancer patients had a significant impact on mortality. In contrast, Osib et al. were unable to show any...
impact of appropriate or inappropriate empirical therapy on mortality or length of hospital stay for patients with *P. aeruginosa* bacteraemia. In that study, the time from culture collection to susceptibility results becoming available was a median of 3.4 days. In an effort to identify the delay in appropriate therapy associated with adverse outcomes, Lodise et al. used CART (Classification and Regression Tree) analysis to identify the delay in therapy associated with increased risk of 30 day mortality. The data used *P. aeruginosa* bacteraemia cases in a retrospective cohort study of 100 immunocompetent patients. The CART analysis critical time was 52 h, with a doubling of mortality if appropriate therapy was delayed beyond this time. Multidrug resistance was associated with a delay in appropriate therapy. There are few data on the impact of specific mechanisms of resistance in *P. aeruginosa* on clinical outcomes; however, a small case series of seven patients infected with metallo-β-lactamase-producing strains indicated very high rates of inappropriate therapy and death.48

*S. aureus*

Methicillin resistance in *S. aureus* is associated with increased mortality in *S. aureus* bacteraemia. Cosgrove et al. performed a meta-analysis of 31 studies involving 3963 patients, in which the pooled analysis indicated a significant increase in mortality in MRSA bacteraemia. The analysis also showed significant study heterogeneity, which suggests that the studies were not measuring a single common effect related to methicillin resistance. A subgroup analysis was performed of studies that had adjusted for confounding variables (severities of illness or co-morbidities), which again showed a significantly increased mortality in MRSA bacteraemia but no significant heterogeneity in the studies. It was proposed that the higher observed mortality was related to: (i) increased pathogenicity of MRSA compared with methicillin-susceptible *S. aureus* (MSSA); (ii) the likelihood that vancomycin is a less effective therapy for MRSA than β-lactams are for MSSA; or (iii) delays in appropriate therapy of MRSA which may impact adversely on outcomes.

There are a significant number of studies addressing the timing of appropriate antibiotic treatment in *S. aureus* bacteraemia. In a retrospective cohort study of the management of *S. aureus* bacteraemia, patients with MRSA infection were less likely to receive appropriate antibiotics in the first 48 h of infection. This however did not affect the risk of death—even after adjustment for age, sepsis or nosocomial infection. Lodise et al. used CART analysis to define a mortality breakpoint between early and delayed therapy in nosocomial *S. aureus* bacteraemia. The critical time was 44.75 h. A multiple regression analysis of the same data indicated that delayed therapy was a predictor of infection-related mortality and longer length of hospital stay. Two similar studies of MRSA bacteraemia have reinforced this conclusion using either retrospective cohort or matched case-controlled study designs. In both studies, delayed appropriate therapy up to 48 h with vancomycin had no impact on mortality. The presence of septic shock made no difference to these conclusions. There are limited studies on the management of MRSA infection in the community, but in one community-based case series, initial empirical antibiotic therapy (often co-trimoxazole) to which the MRSA was susceptible increased the chances of clinical resolution even after controlling for incision and drainage of abscesses or collections or HIV status.25

Although not specifically sought in the BSAC bacteraemia surveillance programme, there is clinical evidence that vancomycin heteroresistance in *S. aureus* has an impact on clinical outcomes in bacteraemia, being associated with persistent fever, bacteraemia beyond 7 days, but also low initial vancomycin trough concentrations (<10 mg/L in the first week of treatment).54

It is clear that not all agents to which bacteria are deemed susceptible in the laboratory have the same clinical outcomes if used in treatment. This is illustrated in two ways: firstly, the comparative clinical outcomes with vancomycin and β-lactams in infection due to MSSA and the debate over the definition of vancomycin susceptibility in *S. aureus*. There is a significant body of clinical evidence that treatment of MSSA bacteraemia, bacteraemic pneumonia, osteomyelitis or infective endocarditis with vancomycin is inferior to the use of β-lactams in terms of mortality, bacteriological outcome or relapsed infection.55–58

The difference remained after controlling for confounding clinical factors or in case-matched studies. Secondly, the vancomycin clinical breakpoint of susceptible ≤4 mg/L (EUCAST), which is widely used in Europe and applied in this surveillance programme, is almost certainly too high.

It is now clear that MICs of <4 mg/L for vancomycin are linked to poor therapeutic outcome in MRSA bacteraemia for MRSA clones prevalent in the USA. Sakoulas et al. studied 30 patients with MRSA bacteraemia derived from clinical trials recruiting patients with infection refractory to vancomycin treatment. For those with MICs of ≥1.0 mg/L, vancomycin was 9.5% effective; for those with MIC ≤0.5 mg/L, it was 55.6% effective. In a second study using a case-matched design, MRSA isolates from bacteraemia with the accessory gene regulatory group II (agrII) gene (*n* = 17) and non *agrII* strains were matched. Time to clearance of bacteraemia was longer if the vancomycin MIC was 2 mg/L compared with ≤1 mg/L. Finally, in a large study of MRSA bacteraemia in Spain (*n* = 414), vancomycin MICs were determined by the Etest and four groups of patients were defined—those who received vancomycin and who were infected with strains for which the initial MICs were 1, 1.5 and 2 mg/L, respectively, and those who received inappropriate empirical therapy. In a multiple regression analysis, infection with an isolate with an MIC of 2 mg/L was associated with adverse outcomes compared with those with lower MICs.

*S. pneumoniae*

There is little doubt that the present definitions of penicillin susceptibility in *S. pneumoniae* have little clinical predictive value in pneumococcal pneumonia. A number of reviews have questioned the presently used clinical breakpoints, pointing out the lack of correlation between β-lactam/penicillin susceptibility results and clinical or microbiological outcomes. This is of course not to state that there is no relationship between penicillin MIC and outcome—merely that the present clinical breakpoints are incorrectly placed, having been developed over 40 years ago when *S. pneumoniae* with raised penicillin MICs were first described. It is also certain that the term penicillin-intermediate *S. pneumoniae* has no clinical implications in terms of therapeutic outcomes in pneumonia. However, penicillin MICs of ≥4 mg/L and cefotaxime MICs of ≥2 mg/L have been significantly associated with mortality in an analysis involving over
5000 patients. In the majority of clinical studies, *S. pneumoniae* strains isolated from patients with pneumococcal pneumonia have penicillin MICs of <4 mg/L, and these studies have not been able to show any impact of penicillin non-susceptibility on mortality, ICU admission, time to fever defervescence, resistance, frequency of suppurative complications and perhaps the need for appropriate antimicrobial chemotherapy.

Pharmacokinetic/pharmacodynamic studies in pre-clinical animal or in vitro models indicate that a penicillin T > MIC of 40% should be related to optimal outcome in man: this implies that the clinically relevant breakpoint for *S. pneumoniae* will vary with dose. This is illustrated in Table 1, which shows Monte Carlo simulations of the commonest intravenous penicillin doses used in some EU countries. In the UK, *S. pneumoniae* with MICs of >1 mg/L are non-susceptible when causing pneumonia according to these considerations.

Macrolide resistance in *S. pneumoniae* has not been studied as intensively as penicillin non-susceptibility; however, the number of cases of microbiologically proven macrolide failure is significant. Macrolide failure in pneumococcal pneumonia has been defined as cases of bacteraemia occurring during outpatient therapy with an oral macrolide (azithromycin, clarithromycin and erythromycin). There is a clear association between erythromycin MIC and failure: failure is significantly more common in strains with MICs >1 mg/L than those with MICs ≤0.25 mg/L.

**Vancomycin-resistant enterococci**

The impact of vancomycin resistance in enterococcal infection outcomes still remains controversial. A number of studies have suggested that in enterococcal bacteraemia, vancomycin resistance is associated with refractory infection, serious morbidity and death. However, whether vancomycin resistance has a direct impact on outcome remains problematic, given the different underlying patient factors in those infected with vancomycin-susceptible or -resistant enterococci. Studies that have corrected for underlying illness (APACHE II score or severity of illness) have not been able to relate vancomycin resistance to outcomes. As might be expected, the impact of appropriate antimicrobial chemotherapy in vancomycin-resistant enterococcal bacteraemia is also unknown.

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### Table 1. Suggested clinical breakpoints for *S. pneumoniae* causing pneumonia

<table>
<thead>
<tr>
<th>Dose, frequency</th>
<th>Country</th>
<th>Penicillin breakpoint based on &gt;90% target attainment of T &gt; MIC 40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4 g, 6 hourly</td>
<td>France, UK</td>
<td>≤1 mg/L</td>
</tr>
<tr>
<td>1.2 g, 6 hourly</td>
<td>UK</td>
<td>≤0.5 mg/L</td>
</tr>
<tr>
<td>0.6 g, 4 hourly</td>
<td>The Netherlands</td>
<td>≤0.5 mg/L</td>
</tr>
<tr>
<td>1.0 g, 8 hourly</td>
<td>Sweden</td>
<td>≤0.12 mg/L</td>
</tr>
</tbody>
</table>

### Table 2. Clinical studies showing the relationship between a pharmacodynamic index and outcome

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pharmacodynamic index</th>
<th>Size of pharmacodynamic index</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin/amikacin/netilmicin</td>
<td>( C_{\text{max}}/\text{MIC} )</td>
<td>&gt;10</td>
<td>Moore <em>et al.</em></td>
</tr>
<tr>
<td>Gentamicin/tobramycin</td>
<td>( C_{\text{max}}/\text{MIC} )</td>
<td>&gt;10</td>
<td>Kashuba <em>et al.</em></td>
</tr>
<tr>
<td>Cefepime</td>
<td>( T &gt; \text{MIC} )</td>
<td>—</td>
<td>Tam <em>et al.</em></td>
</tr>
<tr>
<td>Ceftobiprole</td>
<td>( T &gt; \text{MIC} )</td>
<td>30–50%</td>
<td>Kimko <em>et al.</em></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>( \text{AUC}/\text{MIC} )</td>
<td>&gt;125</td>
<td>Forrest <em>et al.</em></td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>( \text{AUC}/\text{MIC} )</td>
<td>&gt;175</td>
<td>Forrest <em>et al.</em></td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>( C_{\text{max}}/\text{MIC} )</td>
<td>&gt;12</td>
<td>Preston <em>et al.</em></td>
</tr>
<tr>
<td>Gatifloxacin/levofoxacin</td>
<td>( f\text{AUC}/\text{MIC} )</td>
<td>&gt;35</td>
<td>Ambrose <em>et al.</em></td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>( \text{AUC}/\text{MIC} )</td>
<td>&gt;87</td>
<td>Drusano <em>et al.</em></td>
</tr>
<tr>
<td>Linezolid</td>
<td>( \text{AUC}/\text{MIC} )</td>
<td>&gt;100</td>
<td>Rayner <em>et al.</em></td>
</tr>
<tr>
<td>Macrolides*</td>
<td>( T &gt; \text{MIC} )</td>
<td>&gt;85%</td>
<td>Schentag <em>et al.</em></td>
</tr>
<tr>
<td>Tigecycline</td>
<td>( \text{AUC}/\text{MIC} )</td>
<td>&gt;17.9</td>
<td>Meagher <em>et al.</em></td>
</tr>
</tbody>
</table>

*aErythromycin and clarithromycin.*
Why antimicrobial susceptibility and clinical outcomes are linked: a rationale

As little as a decade ago, the relevance of antibiotic susceptibility testing was regarded as ‘not self-evident’, and the value of clinical breakpoints questioned. The success of antimicrobial therapy was suggested to be related to the use of large doses of the antimicrobials and the active innate pathogen defences in the host.

It is now clear that antimicrobial susceptibility testing using a phenotypic test system (MIC or disc zone diameter) can be used with appropriate clinical breakpoints to define resistance, which, as the studies reviewed earlier indicate, for many pathogens and in many clinical environments, is of help in determining appropriate antimicrobial therapy and so achieving improved clinical outcomes.

At first, it may not seem self-evident how a single laboratory-based measurement can be of predictive value in a complex multifactorial clinical environment such as BSI or ICU-related sepsis. The present pharmacodynamic/pharmacokinetic paradigm helps to explain the relationship between MIC (and a subsequent categorization as susceptible or resistant) and clinical outcome. Table 2 lists the pharmacodynamic indices associated with clinical outcomes reported in a large range of clinical studies since the mid-1980s. Although most of these studies were performed in patients treated in hospital or special patient groups, there are also data to support the predictive value of $T > \text{MIC}$ in predicting outcomes with $\beta$-lactams in community infection. These human studies are supported by a wealth of information in animal and in vitro pharmacodynamic models. Whichever pharmacodynamic index is linked to drug outcome, it is a mix of drug pharmacokinetics such as dose and volume of distribution that determines $C_{\text{max}}$, dose, clearance and absorption that dictate AUC or $C_{\text{max}}$, and plasma elimination that determines $T > \text{MIC}$, with a measure of drug potency (MIC). Hence, the size of any pharmacodynamic index ($C_{\text{max}}$/MIC, AUC/MIC or $T > \text{MIC}$) is determined by variation in drug pharmacokinetics (dose, $V$, clearance, absorption and protein binding) and variation in the pathogen MIC. A low drug exposure in blood (low dose, large $V$, high clearance, poor absorption and low free drug fraction) combined with a high MIC will result in a low value for the pharmacodynamic index and is likely to be associated with increased risk of poor clinical outcome.

In most situations, there is much more variability among isolates in their bacterial susceptibility to a specific antibiotic than variation in host-based drug handling. Hence, the range of potential MICs is much wider than the range of possible AUCs. Hence, an increase in MIC will quickly reduce the pharmacodynamic index to such a value that a clinical response is very unlikely even for those patients with the most favourable pharmacokinetics. Therefore, changes in the MIC are the main reason for large changes in the pharmacodynamic index such that a favourable clinical response is unlikely to occur. In these situations, MIC alone (or its surrogate, zone size) will predict the outcome. In contrast to this more common situation, sometimes the pathogen MIC is such that pharmacokinetic variation may result in favourable outcomes. Such variability is likely to be important in situations in which the MIC is raised, but not to a great degree: $S$. aureus strains with vancomycin MICs of 2–4 mg/L, many anti-pseudomonal agents, or the use of piperacillin/tazobactam to treat tissue-based infections due to ESBL-producing Enterobacteriaceae.

The potential interactions between pathogen, susceptibility and pharmacokinetics are illustrated in Figure 1. The use of wild-type cut-offs as clinical breakpoints may predict clinical outcome, but often does not, for example, with penicillin and $S$. pneumoniae.

Conclusions

The last decade has seen the publication of a large number of clinically based studies showing the benefit of the use of appropriate antimicrobial chemotherapy in a range of settings and for a range of pathogens. Fundamental to appropriate chemotherapy is the determination of bacterial resistance to antibiotics—this is performed in phenotypic laboratory-based testing systems, such as disc susceptibility testing or MIC determination. These studies have helped to show the predictive value of laboratory-based susceptibility testing and also underlined the importance of well-constructed and -executed antimicrobial surveillance.
programmes determining the burdens of antibiotic resistance in relevant clinical situations.

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References


Outcomes of therapy


