Approaches to improving antibiotic management

New information is available to improve antibiotic outcomes in severe sepsis where increasing resistance and reducing novel compound development make reaching the right decisions ever more difficult and important.

There is widespread recognition that, over the last quarter of a century, while increasing problems with various challenges of antimicrobial resistance have evolved (Masterton, 2005a,b), so the pipeline of new agents to address these threats has diminished (Spellberg et al, 2004). The Food and Drug Administration in the United States saw approval of new antibacterial agents reduce by 56% from 1998–2002 compared to 1983–7. In 2004 new antibacterial agents constituted only six of 506 drugs disclosed to be in development (Spellberg et al, 2004) and even now, when the drug development tide is stated to be turning, it will be 10–15 years before any benefits of this are seen in clinical practice (Theuretzbacher, 2009).

Every effort must be made to maximize the benefits of the existing antimicrobial armamentarium both in terms of clinical efficacy as well as against the development of antibiotic resistance. The starting position must be that antibiotics should only be used when their benefit is proven. As a result of a UK government initiative to minimize antibiotic resistance development in England general practice prescribing of antibiotics to children with upper respiratory tract infections was halved from 1993 to 2003 without detriment to clinical outcomes (Sharland et al, 2005). However, it is in hospital where the greatest need for antibiotic clinical efficacy and the greatest peril from resistance is felt and this article will therefore focus on current developments in prudent prescribing for maximum impact with minimum detriment.

Antimicrobial stewardship

Several authorities have recognized the need to maximize and protect the present antibiotic armamentarium and the Infectious Diseases Society of America published guidelines based upon a systematic review of the evidence for developing an institutional programme to enhance antimicrobial stewardship (Dellit et al, 2007). The guidelines identified eight elements within core active antimicrobial stewardship strategies, to be based on local practice patterns and resources. These were:

1. Education
2. Guidelines
3. Antimicrobial cycling
4. Antimicrobial order forms
5. Combination therapy
6. De-escalation
7. Dose optimization
8. Intravenous to oral step down therapy.

Inevitably the strength of a recommendation and the quality of evidence vary significantly across the elements that were assessed. However, dose optimization based on individual patient characteristics, causative organism, site of infection, and pharmacokinetic and pharmacodynamic characteristics of the drug was found to be an important part of antimicrobial stewardship and was towards the higher end of the recommendation and evidence quality scales.

Dose optimization

Intellectually clinicians understand that antimicrobials exert their effects through two key components. The first of these is the pharmacokinetic properties of the agent – essentially a description of the time course of the drug in the different tissues or compartments of the body – and the second is the pharmacodynamic interaction between the antibiotic and the organism – effectively the 'drug:bug' concentration *vs* effect relationship.

From this description it is apparent that an antibiotic's effect will depend upon the agent chosen, the pathogen it is treating, the site of infection and the concentration of the antibiotic achieved at that site according to the dose given and its route of administration. However, this is rarely recognized in normal practice where therapy is based upon a laboratory result indicating the susceptibility of the pathogen in a highly artificial environment and the licensing information of the compound concerned. Given the restrictive and exacting requirements of licensing processes this last invariably depends upon traditional approaches to therapy that are conservative and supported by decades of precedence. Nevertheless practices are beginning to change and the relevant international authorities are now setting laboratory breakpoint definitions for antimicrobials with an eye to the pharma-

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cokinetic and pharmacodynamic parameters of the compound so that these relate to a specific drug and pathogen in a specific infection type.

Similarly the pharmacokinetic distribution effects of antibiotics are affected by disease and iatrogenically by interventions, with this being most pronounced in the sickest patients in the intensive care unit (Scaglione and Paraboni, 2008; Roberts and Lipman, 2009).

Different antibiotic types act, pharmacodynamically, in different ways. The measurements that describe these pharmacodynamic properties are well understood (*Figure 1*). The pharmacodynamic properties of antibiotics that best describe killing activity are time-dependence, concentration-dependence, and persistent effects. These properties should therefore guide use towards therapeutic approach goals (*Table 1*), although added complexities exist in that the numeric value to be sought varies with antibiotic class and subclass (Scaglione and Paraboni, 2008).

Figure 1. The dimensions describing pharmacodynamic function. AUC = area under the concentration–time curve; C_{max} = maximum plasma concentration; MIC = minimum inhibitory concentration.

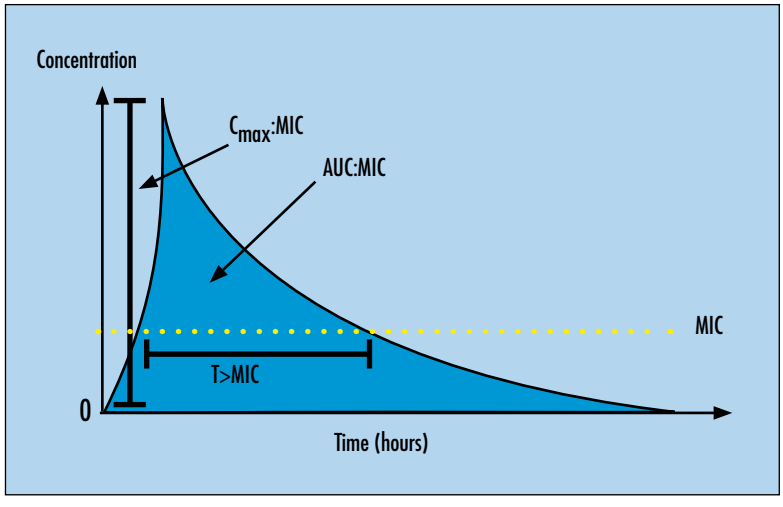


Table 1. Defining therapeutic goals through pharmacodynamic parameters

Type of pharmacodynamic activity	Pharmacokinetic/ pharmacodynamic parameter	Antibiotic types	Therapy goal
Concentration-dependent killing with significant persistence	24h-AUC/MIC Peak/MIC	Aminoglycosides Daptomycin Fluoroquinolones Ketolides	Maximize concentrations
Time-dependent killing with minimal persistence	T>MIC	Carbapenems Cephalosporins Erythromycin Linezolid Penicillins	Maximize exposure duration
Time-dependent killing with significant persistence	24h-AUC/MIC	Azithromycin Clindamycin Oxazolidinones Tetracyclines Vancomycin Tigecycline	Maximize concentrations and amount of drug

AUC = area under the curve; MIC = minimum inhibitory concentration

The limitations of one-dimensional traditional laboratory susceptibility reporting have led to efforts to devise new report types of greater relevance to the clinician. One approach has been the concept of target attainment. The OPTAMA programme uses extensive microbiology data capturing from surveillance work, the pathogen spectrum of given conditions and their susceptibilities, combining this with pharmacokinetic and dosing variables to generate a simulation based on clinical reality to produce a probability calculation for the target attainment of the clinical goal, e.g. condition-specific bactericidal target outcomes for different geographical regions, organisms and antibiotic regimens (Koomanachai et al, 2009). The goal of this target attainment is to be able to tell clinicians treating patients with severe sepsis the percentage probability of any given antibiotic regimen achieving clinical success against any given infection. To date, although this work has produced interesting findings in terms of demonstrating that susceptibility does not equate to target attainment (Masterton et al, 2005) and that increasing resistance over time can disproportionately affect target attainment as compared to susceptibility (Crandon et al, 2009), there are as yet no good clinical trials demonstrating the utility of the approach in practice. However, a retrospective study using this approach to assess management of complicated skin and soft tissue infections demonstrated an excellent correlation between target attainment and the actual clinical and microbiological outcomes so the stratagem appears to hold promise (Kuti et al, 2006).

Dosing optimization

If drug and dose selection are better identified from the above approaches then the third element of potential improvement is in determining the best mechanism of administration. From *Table 1* it follows that where time dependency is a critical criterion for pharmacodynamic activity then extended or continuous infusion of such agents to maximize the time of drug concentration above the minimum inhibitory value ought to benefit outcome. Many studies exploring this approach have now been reported with the vast majority, understandably in view of its principal time-dependent association, involving the beta-lactams. Indeed, since continous infusion of beta-lactam antibiotics is potentially most beneficial in serious sepsis, much of this work has focused on carba-penems as the class leader for such conditions (Masterton, 2009).

An early meta-analysis of randomized controlled trials comparing continuous *vs* intermittent intravenous administration of antibiotics identified nine includable

randomized controlled trials investigating beta-lactams, aminoglycosides and vancomycin (Kasiakou et al, 2005). Although the clinical failure in the continuous infusion patients was lower this was not a statistically significant difference (pooled odds ratio=0.73, 95% confidence interval=0.53–1.01) other than in a subset analysis where the same total daily antibiotic dose was used in both intervention arms (odds ratio=0.70, 95% confidence interval=0.50–0.98). There were no statistically significant differences in mortality or nephrotoxicity.

A more recent meta-analysis that explored only beta-lactams found fourteen eligible randomized controlled trials involving 846 patients (Roberts et al, 2009a). Again continuous infusion was not associated with an improvement in clinical cure (odds ratio=1.04, 95% confidence interval=0.74–1.46) or mortality (odds ratio=1.00, 95% confidence interval=0.48–2.06). It was conjectured that the reason that continuous infusion of beta-lactam antibiotics led to the same clinical results as higher dosed bolus administration was a result of bias created by a higher dose of antibiotic in the bolus group in the randomized controlled trials and because many of the randomized controlled trials only recruited patients with a low acuity of illness.

A modelling study captured well the dynamic interplay of physiological function, dose, infusion interval and minimum inhibitory concentration for the new carbapenem, doripenem (*Table 2*) (Van Wart et al, 2009). This demonstrated how increasing the dose and the infusion duration can be used to cover organisms of increasingly less susceptibility and how this relates to renal function. There is some evidence that these theoretical effects hold true in clinical practice.

In a patient study exploring meropenem it was found that continuous infusion maintained higher median trough concentrations, in both plasma (intermittent bolus 0 *vs* infusion 7 mg/litre) and subcutaneous tissue (0 *vs* 4 mg/litre) (Roberts et al, 2009b). Pharmacodynamic target achievement against less susceptible pathogens such as *Pseudomonas aeruginosa* and *Acinetobacter* species was better by extended or continuous infusion.

The logical next step is to look for evidence of improved clinical outcomes when using carbapenem by extended infusion. In a trial involving ventilator-associated pneumonia patients that investigated meropenem combined with tobramycin by continuous (1 g over 360 min every 6 hours), against intermittent infusion (1 g over 30 min every 6 hours) the continuous infusion arm showed a greater clinical cure rate (odds ratio=6.44, 95% confidence interval=1.97–21.05) (Lorente et al, 2006). However, the number of patients involved was small (42 *vs* 47 respectively).

A much larger study (531 patients), also of patients with ventilator-associated pneumonia, has been reported for doripenem (Chastre et al, 2008). Cases were randomly assigned to doripenem 500 mg every 8 hours via a 4-hour intravenous infusion or imipenem 500 mg every 6 hours or 1000 mg every 8 hours via 30- or 60-minute intravenous infusions respectively for 7–14 days. Overall doripenem was found to be non-inferior to imipenem (lower boundary of 95% confidence interval around the difference between treatments ≥20%) with clinical cure rates of 68.3% *vs* 64.2% respectively in clinically evaluable subjects. Although there were trends of superiority for doripenem in respect of *P. aeruginosa* and microbiological cure these did not reach statistical significance. However, clinical cure rate was higher with doripenem than imipenem in sub-analyses against older ages and higher disease severity scores. Furthermore 18% (5 of 28) of *P. aeruginosa* isolates had minimum inhibitory concentration ≥8 μ/ml at baseline or following therapy in the doripenem arm compared with 64% (16 of 25) in the imipenem treatment group (*P*=0.001), indicating a possibility of some resistance development protection associated with doripenem extended infusion.

Table 2. Variable dynamics *vs* target attainment outcome for doripenem

Infection status		Antibiotic variables	Outcome	
Minimum inhibitory concentration (mg/litre)	Renal function	Dose (mg)	Infusion duration (hour)	Probability (%) of pharmacokinetic/ pharmacodynamic target attainment
≤1	Normal	500 three times a day	1	≥90
≤4	Normal	500 three times a day	4	≥90
≤8	Normal	1000 three times a day	4	≥90
≤4	Moderately reduced	250 three times a day	1	≥93
≤4	Moderately reduced	250 three times a day	4	≥99
≤8	Moderately reduced	1000 twice a day	4	100
≤4	Severely reduced	250 twice a day	1	≥99
≤4	Severely reduced	250 twice a day	4	100

MIC = minimum inhibitory concentration. Adapted from Van Wart et al (2009)

Resistance

There is an increasing interest in seeking to use pharmacokinetic and/or pharmacodynamic effects to minimize the development of resistance (Rybak, 2006). In fluoroquinolones the ratio of the area under the cost to the minimum inhibitory concentration of drug exposure has been related to resistance development with values >100 providing protection against the development of resistance (Thomas et al, 1998). Although some studies indicate potential benefits from this approach among other antibacterial classes (Chastre et al, 2008), there are insufficient data to reach a clear conclusion.

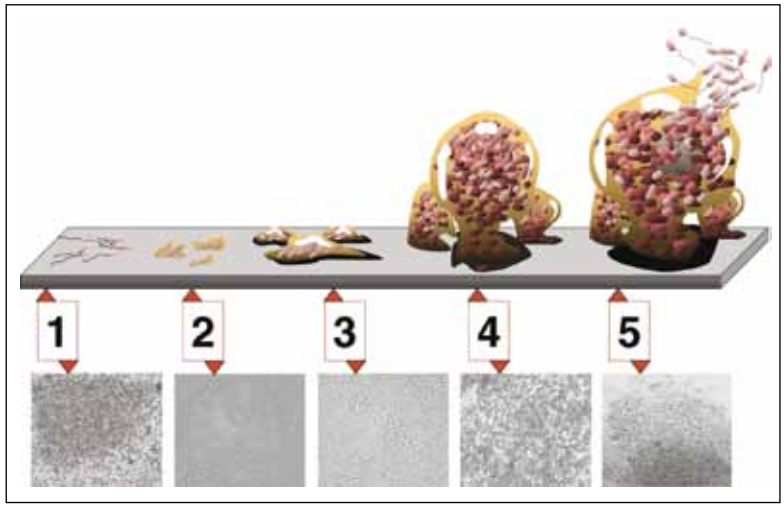
A descriptor, the mutant prevention concentration, has been coined to depict concentrations above which resistance development is unlikely and further work is needed to fully characterize target concentrations that prevent resistance (DeRyke et al, 2006).

Cost effectiveness

A different dimension of the pharmacokinetic and pharmacodynamic therapeutic approach is its cost effectiveness and, unlike clinical benefit realization, this aspect is well established. By using the impact of infusion therapy it is possible to reduce the drug dose deployed and so reduce costs. In an extended infusion study of meropenem in ventilator-associated pneumonia a drug cost reduction of 35% was achieved (Wang, 2009) while in serious sepsis patients a 25% reduction of piperacillin/tazobactam was realized (Roberts et al, 2009c).

In summary, whereas the cost effectiveness of these new approaches can clearly produce real and significant drug savings the clinical benefits are to date less well demonstrated. All the evidence suggests improved patient outcomes with less resistance generation but the literature lacks large, well-conducted, prospective, randomized studies in serious sepsis, which must be the proving ground. Only the new carbapenem, doripenem, has a licensed indication for extended infusion therapy and it is doubtful from a commercial perspective, given the business life cycles for the older antibiotics of interest, whether other companies will be prepared to fund such trials. This must not prevent the necessary rigorous testing of the above paradigm, although it can be argued that for economic reasons alone its introduction should progress.

Figure 2. Stages in the formation of a biofilm.



Biofilms: the next challenge?

Even the above more sophisticated approaches are an oversimplification of the actual world of the pathogen and the body. In a large number of septic states, e.g. cystic fibrosis, otitis media, endocarditis, intravascular line sepsis and foreign body implantation sites, organisms exist not in a freely antibiotic penetrable world but protected by an all-enveloping matrix.

In response to this the effect of a biofilm mode of growth on in-vitro sensitivity testing is beginning to be explored. Biofilms are complex communities of bacteria and bacteria existing in different parts of the biofilm do so in differing metabolic states (*Figure 2*). When living in biofilms bacteria tend to be more resistant to antibiotics. This may be because of their metabolic state and/or the presence of large amounts of extracellular matrix, which is produced by the cells in the biofilms and prevents antibiotic penetration. In environmental systems biofilms are actually the normal form for many bacteria rather than the planktonic growth seen when organisms are grown and tested under standard laboratory conditions. In the lung of patients with cystic fibrosis microscopic evidence shows bacterial aggregates present both in the sputum and colonizing the surface lung airways (Bjarnsholt et al, 2009). *P. aeruginosa* in sputum from cystic fibrosis patients also produces biofilm signalling (quorum sensing) molecules in ratios similar to those produced by laboratory biofilms (Singh et al, 2000).

In other conditions such as urinary tract infection there is evidence that uropathogenic *Escherichia coli* invades urinary epithelium and establishes 'pods' or biofilms that help it evade the host immune response. Organisms within these pods are enmeshed in an extracellular matrix and produce type 1 pili and antigen 43, factors known to participate in biofilm development (Anderson et al, 2003; Justice et al, 2004).

Different therapeutic options may need to be considered for the effective treatment of biofilm-associated conditions. Combinations of either antibiotics chosen to act on different regions of the biofilm, such as colistin and tobramycin for *Pseudomonas* biofilms (Herrmann et al, 2009) or the addition of compounds such as deoxyribonuclease (DNase), which degrades the extracellular matrix, enhances the effect of antibiotics and results in decreased biofilm biomass and numbers of colony forming units (Tetz et al, 2009). Until we can fully realize how to most effectively kill organisms in biofilms we cannot do our best for patients and this work needs to build on our present better understandings.

Conclusions

The war on antimicrobial resistance development will be fought on many fronts. Battlefields will exist with the emergence of new antibiotics, the impact of infection control measures and adopting active antimicrobial stewardship. If clinicians are to win this conflict then optimizing antimicrobials use via the approaches described above must become a major campaign that we are all involved in since this is a key weapon that will both reduce resistance development and improve clinical outcomes. **BJHM**

Figure 2 *is reproduced from http://commons.wikimedia.org/wiki/File:Biofilm.jpg.*

Conflict of interest: Dr RG Masterton has received honoraria for speaking and advisory work from Abbott, AstraZeneca, Pfizer and Wyeth. Dr C Williams has received honoraria for speaking and advisory work from Janssen Cilag and Astrellas, he also has unrestricted educational grants from Pfizer, Gilead Sciences and MSD.

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KEY POINTS

- By prescribing antimicrobials well in severe sepsis clinicians will maximize patient outcomes while minimizing resistance development.
- Optimization of antimicrobial delivery through selecting the best dose and route of administration is a key part of antimicrobial stewardship.
- More information is needed to enable the sepsis challenge of biofilms to be most effectively addressed.