



Antibiotic resistance: the perfect storm

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ARTICLE INFO

Keywords:

Antibiotic stewardship
Antibiotic resistance
Prescribing policy
Meticillin-resistant *Staphylococcus aureus*
Klebsiella pneumoniae
carbapenemases

ABSTRACT

The worldwide epidemic of antibiotic resistance is in danger of ending the golden age of antibiotic therapy. Resistance impacts on all areas of medicine, and is making successful empirical therapy much more difficult to achieve. Antibiotic choices are often severely restricted, and the pipeline of new antibiotics is almost dry. Resistance cannot be prevented, but its development and spread can be slowed. One of the tools at our disposal is maximising diversity in our prescribing. The advent of tigecycline, the first in a new class of intravenous antibiotics, is important in this context, giving us a further monotherapy option for severe infections. Another strategy is seriously to curtail the large amount of unnecessary antibiotic use in many areas of life, not only medical practice. The various aspects of this strategy are briefly reviewed.

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1. Introduction

The worldwide epidemic of antibiotic resistance is touching all patients and medical practitioners. It is an ecological disaster of unknown consequence and, unlike global warming, has no obvious solution. The huge scale of antibiotic use is well described, but reversing entrenched prescribing practices is extremely difficult.¹ The antibiotic pipeline has almost run dry, with no new classes of agent expected to be in use in the next 20 years.² Antibiotic-resistant bacteria are increasingly seen to be just as virulent as their sensitive counterparts, and their genetic adaptability gives bacteria a huge advantage over mankind.³

In this short review I will enlarge upon each of these issues and suggest ways in which we can hope to at least slow the resolute onslaught of resistance. In particular, I will discuss prescribing strategies as they might influence resistance. Just as important, I will show that antibiotic stewardship might also be a tool to reduce hospital-acquired infection, at a time when we are struggling to cope with it using conventional infection-control policies.

2. The epidemic of antibiotic resistance – how are we coping?

The global emergence of different clones of meticillin-resistant *Staphylococcus aureus* (MRSA) has arguably been

the biggest setback in the history of antimicrobial therapy.⁴ MRSA has caused serious problems in the empirical use of all the major classes of antibiotics in common use – the cephalosporins, penicillins, carbapenems, quinolones and aminoglycosides. Moreover, MRSA has not replaced meticillin-susceptible *S. aureus* (MSSA), but is an additional burden of infection, often doubling or trebling the number of clinical staphylococcal infections, whether in the hospital or the community.⁵

Outcomes are worse for MRSA infection than for MSSA, for complex reasons including inappropriate empirical treatment.⁶ Possibly the major cause of this inferior outcome in MRSA infection is the reliance on glycopeptides, which have long been known to be suboptimal for MSSA infections.⁷ Indeed vancomycin, launched in 1958 on the evidence of successful treatment in just a handful of patients, was soon dropped from routine clinical use when the semisynthetic penicillins were introduced in the 1960s. Unfortunately, we still await the development of equivalent drugs for the treatment of MRSA. All new agents, and those likely to be marketed in the foreseeable future, have significant drawbacks.

The situation in Gram-negative bacteria is no less serious, and even more complex. There seems no end to the number of β -lactamases that have evolved (Fig. 1), and the worldwide spread, first of expanded-spectrum β -lactamases (ESBL) and now the carbapenemases, is causing serious concern. ESBL rates in particular seem to have increased greatly in the past 3 or 4 years.⁸ Moreover, linkage on mobile genetic elements

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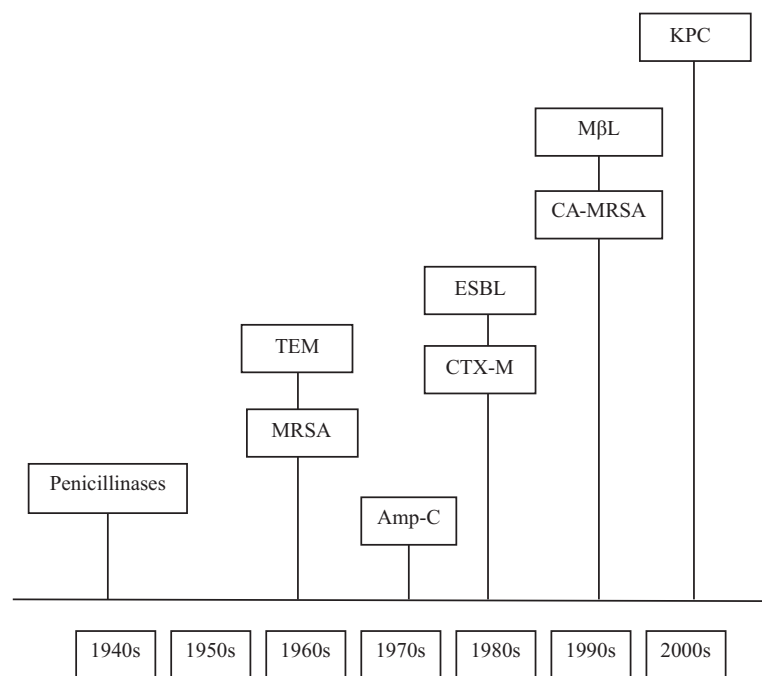


Fig. 1. Evolution of resistance to β -lactam antibiotics. Amp-C, chromosomal ampicillinase; CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; CTX-M, cefotaximase; ESBL, expanded-spectrum β -lactamases; KPC, *Klebsiella pneumoniae* carbapenemases; M β L, metallo- β -lactamases; MRSA, methicillin-resistant *S. aureus*; TEM, TEM β -lactamase.

to aminoglycoside- and/or quinolone-resistance determinants is ensuring a rapid rise in multidrug resistance, with extreme and even pan-drug resistance now becoming a reality.⁹ CTX-M-type ESBL are spreading this hospital problem into the community, challenging the oral treatment of many community-acquired urinary tract infections, as these strains are also often resistant to quinolones, tetracyclines and trimethoprim–sulfamethoxazole.¹⁰ Metallo- β -lactamases were originally described in Japan, where early carbapenem use was highest, and emerged in Europe over a decade ago. They are now found globally, and render essentially all β -lactam agents (except sometimes monobactams) useless.¹¹ Often there is cross-resistance to aminoglycosides, quinolones and other classes, necessitating the use of polymyxins or, perhaps, fosfomycin. Resistance to colistin is increasingly described.¹²

Whether it be a resistant Gram-positive or Gram-negative organism that is causing a therapeutic problem, one of the most likely causes is prior exposure of that patient to one or more broad-spectrum antibiotics.¹³ Whether it is MRSA, vancomycin-resistant enterococci or a resistant/multiresistant Gram-negative organism, it is likely that the patient will have been given a quinolone or broad-spectrum β -lactam, often a third- or fourth-generation cephalosporin, which will increase the chances of acquisition two- or threefold. It is not certain whether the newer cephalosporins are really more likely to select for resistance than other broad-spectrum agents, or whether their frequent incrimination merely reflects common use, as they are often the single most commonly used class of drugs in hospitals. Recently, Hsueh in Taiwan described 26 pan-resistant *Pseudomonas aeruginosa* (PDRPA) strains resistant to all agents available in that country, although still susceptible to colistin.¹⁴ Each patient had received a carbapenem or new cephalosporin, alone or with an aminoglycoside or quinolone, before isolation of the PDRPA. The isolates were polyclonal,

but mainly contained *bla*_{VIM-3}, suggesting that horizontal transmission of this gene may have occurred.

Selection of resistance to one antibiotic by another, perhaps unrelated, agent can be explained by carriage of multiple resistance determinants. Exposure to any one encoded antibiotic can maintain the selection pressure for continued carriage of resistance to all the antibiotics thus encoded.

3. The burden of antibiotic resistance

The burden of antibiotic resistance has been estimated in several studies and reviews.^{6,15} Simplistically, mortality is often double that following infection with equivalent susceptible organisms, but there are factors to consider that probably mean this is an underestimate.

Firstly, resistant organisms such as MRSA and *Clostridium difficile* often represent an additional burden of infection.¹³ *C. difficile* is clearly associated with antibiotic use, but the situation is often less clear for other organisms. With MRSA, however, there is good evidence that MSSA infections continue at the same or even higher rates;¹⁶ they have not been replaced by MRSA. I am not aware of such clear-cut evidence for an absolute increase in the number of infections with Gram-negative organisms, but a study from 40 years ago suggests this may also be true.¹⁷ Where all antibiotic prescribing was banned in a desperate attempt to control a multiresistant *Klebsiella* strain on a neurosurgical unit, not only did the outbreak strain disappear, but the overall incidence of infection decreased significantly, and no one died of untreated infection. So it is clear that antibiotic use often adds to the overall burden of infection, at least in the hospital, and not just the burden of resistance. Secondly, the outcome of treatment with second- or third-line agents may be inferior, and yet they are often used as empirical

Table 1. Core elements of antimicrobial stewardship programmes

Tactic	Level of evidence ^a	Comment
Guidelines and clinical pathways	A-I	Core activity, but implementation plans are critical
Education	A-III	Critical, but must be ongoing and interactive
Antimicrobial cycling/mixing/diversity	C-II	Might work if done very frequently Diversity probably best
Antimicrobial order forms	B-II	Focuses decision making Shortens duration of treatment
PK/PD dose optimisation	A-II	Improves outcome Prevents resistance
Combination therapy	C-II	Increases antibiotic exposure Mainly theoretical benefit Likely to be most beneficial at start of treatment
Streamlining or de-escalation	A-II	Reduces use of broad-spectrum agents
Intravenous to oral switch	A-III	Reduces costs and length of intravenous access May not help with resistance per se

^a Strength of recommendation: A, good evidence to support a recommendation for use; B, moderate evidence to support a recommendation for use; C, poor evidence to support a recommendation for use.

Quality of evidence: I, evidence from ≥ 1 properly randomised, controlled trial; II, evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time-series; or from dramatic results from uncontrolled experiments; III, evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

therapy when resistant organisms become relatively common. This may well lead to inferior outcomes, even in susceptible infections, as has often been demonstrated with vancomycin in the treatment of MSSA infection.⁶ In addition, the costs of these agents are often much greater. Finally, as their use becomes the norm, studies comparing outcomes will show less difference between susceptible and resistant infections.

4. Antibiotic use and collateral damage

This association between antibiotic consumption and resistance is frequently seen at a patient level in case-control studies, and also at a hospital and community level.¹³ Its reversal can be demonstrated by reduced consumption, although this is usually only a relative reduction – reduced use of one agent is associated with increased use of another.¹⁸ This is called ‘squeezing the balloon’ and often results merely in swapping one resistance problem for another.¹⁹ The generally elusive challenge in antibiotic stewardship is to reduce total consumption, the only sure way to delay the development of resistance.

This resistance is, of course, an unintended consequence of antibiotic therapy, as is *C. difficile* infection. Unfortunately, it threatens the golden age of antibiotic therapy, which has seen the development of aggressively immunosuppressive diagnostic and therapeutic procedures only because of the protective power of antibiotics. This success has led to a dismissive attitude to infection, and a lack of appreciation of the need for scrupulous hygiene, which is now coming back to haunt us. The unparalleled problems of hospital-acquired infection and antibiotic resistance clearly go hand-in-hand and feed off each other, sustained by the ever-increasing spiral of therapeutic empiricism that follows the belief that antibiotics are a cure-all.²⁰ It is all too clear now that there is much collateral damage from these wonder-drugs, and that we must not take them for granted any more. Not only must we relearn the principles of hospital hygiene that were so methodically worked out in the 18th and 19th centuries, when there were

no antibiotics,²¹ but we must develop new strategies for diagnosing and treating infections.

One further, not often appreciated fact that must be mentioned is the propensity for antibiotics not only to select for resistant bacteria, but also to aid their transmission and increase their virulence. This not only causes more infections, but also infections of increased severity, as in the case of MRSA in both the hospital and community.¹³

5. Antibiotic stewardship programmes

So far, initiatives to speed the development of new antimicrobials, such as extending patent life, better approval processes, purchase commitments and tax credits have not yielded notable success.² Thus we have no alternative but to use antibiotics more wisely. Whereas antibiotic resistance is inevitable, the current rate of its development and spread is not.

Antibiotic stewardship can, however, offer more than an effect on resistance. It can also reduce pharmacy costs, toxicity and the acquisition of potentially pathogenic bacteria by preserving the normal protective bacterial flora. Stewardship programmes are of two main types, restrictive and educational. Whereas the former can have a rapid effect, the limited data available suggest it is harder to maintain long-term benefit with these than with educational programmes.²² These are often based on audit and feedback. Supplementary strategies are many, and include guidelines, pathways, cycling/rotation, order forms, automatic stop, streamlining/de-escalation, electronic decision support, PK/PD dose optimisation, combination therapy and oral switch.²³ All of these interventions have roles, although robust evidence is lacking for some, and evidence that any of them can reduce resistance is sparse (Table 1).²³

One of the main problems with current stewardship strategies is their tendency to encourage homogeneity of antibiotic prescribing, which results from the use of a limited number of agents listed in local formularies. This

is a traditional approach to managing prescribing, which might save money and lead to familiarity with commonly prescribed agents, but is probably not the best way to slow resistance. Mathematical models, and clinical, laboratory and animal-model experience, show that combination therapy and diversity are the best ways to slow the development of resistance.^{24,25} Combination therapy has certainly proved successful in the management of tuberculosis and HIV infection, but has many drawbacks limiting its widespread application for this purpose in most bacterial infections. Of course, there are other reasons for combining agents, most importantly broadening the spectrum of empirical therapy. Synergy is occasionally important, but combination therapy will usually increase the antibiotic exposure of the normal flora and add to the overall ecological damage, without demonstrating any clinical benefit.

Diversity of prescribing can be attempted by cycling, but this remains of unproven benefit, possibly because of the limited number of classes of antimicrobial agents actually available.²⁶ Mathematical models suggest that if cycling is to work then it should be done as frequently as possible, even daily. Probably the best approach is individuality – patient-directed prescribing based on susceptibility results (where available). In essence, this is mixing or heterogeneity, attaining maximum diversity. In this context we can welcome the introduction of tigecycline as a new class of antibiotic available for the treatment of serious hospital infections with, for the moment at least, little cross-resistance with other classes and little potential for causing *C. difficile* infection.

6. Conclusions

It is difficult to know what the future holds. In the absence of major new classes of antibiotics, at least in the foreseeable future, we have to reassess and increase the level of education available to medical students. Lifelong re-education of prescribers is probably also required, and should perhaps be part of revalidation/accreditation. Perhaps antibiotic prescribing should only be possible by doctors and other health professionals who have been certified as competent, probably after undergoing educational programmes in the field. Gone should be the days when all doctors can prescribe what they like, when they like. Hopefully, other areas of research will prove fruitful, such as antivirulence factors, agents to reverse resistance, and phage therapy. Otherwise the bugs will surely reign supreme, holding back developments in modern medicine.

Funding: IMG received an honorarium for writing this article from Wyeth Pharmaceuticals.

Competing interests: IMG has received lecture fees, travel grants, research income and/or consultancy fees from several major pharmaceutical companies, including Wyeth and Pfizer.

Ethics approval: Not required.

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