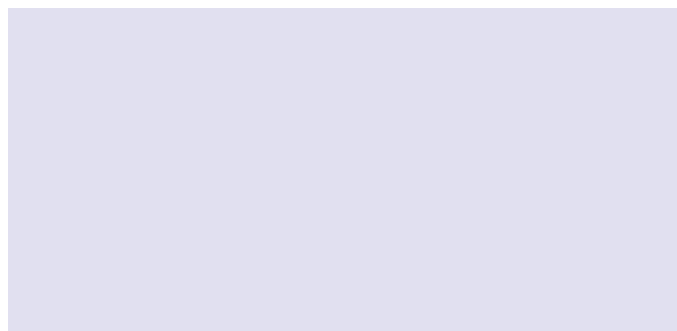


INFECTIOUS DISEASES

— the need for new antibiotics

By JONATHAN COOKE, PHD, MRPHARMS

While antimicrobial drug resistance increases, there is a lack of new treatments coming to the market. The first article in this month's special feature looks at why there is a need for new antibiotics

Electron micrograph image of methicillin resistant *Staphylococcus aureus*

DR KARL LOUNATMA/SPL

What went wrong with antibiotics, was a question posed in a leading article in the *BMJ*. It offered suggestions on ways to promote the rational use of antibiotics in order to stem the development of microbial resistance and to save money. This article appeared in 1984.¹

What has changed? Over the previous 20 years there had been a proliferation in the introduction of new antibiotics on the UK market, particularly the β -lactams, notably penicillins and cephalosporins.

Panel 1 (p266) shows the different agents listed over time in the British National Formulary (BNF). Of particular interest is the increase and then decline in the β -lactam antibiotics over four decades of use.

After introduction these new agents initially addressed the problems that were seen in clinical practice of the development of antimicrobial resistance. However, they were subsequently rendered less effective either by the development or transfer of resistance to micro-organisms that caused specific diseases or by newer pathogens evolving and new infection challenges. Thus penicillin is now regarded as being ineffective for staphylococcal infections, as is ampicillin for cystitis.² The strong link between antimicrobial use and the development of resistance has been demonstrated recently in a case-linked study. These results support efforts to reduce unnecessary antibiotic prescribing in the community and

show the value of individual patient data for research on the outcomes of prescribing.^{3,4}

In the UK it has usually been the practice to use antibiotics in a more conservative way. Formularies and guidelines are in common practice and narrow spectrum agents are promoted initially with powerful agents kept in reserve. A stepwise approach to treatment is advocated, restricting use of the more powerful agents to those who have knowledge of local resistance patterns and the place of these agents in practice. This approach is one that is often advocated by governments,^{5,6} professional bodies and the World Health Organization. Pharmaceutical manufacturers are also recognising the need to work with health care systems to preserve antibiotic effectiveness for public protection.⁷

In a number of centres the cycling of currently available antibiotics to reduce resistance has been employed. However, for cycling strategies to be successful, their implementation must have a demonstrable impact on the prevalence of resistance determinants already dispersed throughout the hospital and associated health care facilities. Over the next decade, new studies with carefully designed outcomes should determine the usefulness of antibiotic cycling as one control measure for nosocomial resistance.⁸ In the US a pharmacist-facilitated restriction programme in a large teaching hospital was shown to produce a dramatic reduction in ceftazidime use with judicious use of other antipseudomonal antimicrobials, which resulted in reduced resistance of *Pseudomonas aeruginosa* to other β -lactams.⁹ In another study removal of an antimicrobial restriction policy resulted in increased use of and higher expenditures for previously restricted agents, as well as an increase in the inappropriate use of at least one agent.¹⁰ In a Dutch study a policy of restrictive

antibiotic prescribing and a national aggressive approach to dealing with MRSA (methicillin resistant *Staphylococcus aureus*) was claimed to lead to a low prevalence of the organism among hospital admissions.¹¹

While the evidence appears to be compelling for these approaches the ability to be successful in practice is sometimes disappointing due to a variability of effective formulary implementation.¹²

An alternative to the minimalist approach is to hit infections hard with powerful agents but stop them quickly before resistance has had time to develop. This approach is frequently advocated in high-risk areas such as transplantation and severe immunosuppression. This has been usually advocated by some manufacturers of the newer antibiotics and has often been the practice in countries that do not operate a predominantly socialised health care system, eg, the US.

WHY DO WE NEED NEW DRUGS?

Despite a reduction in the numbers of prescriptions for antibiotics in primary care over recent years resistance rates for some organisms, eg, erythromycin in pneumococci, have remained steady,¹³ while for others, eg, fluoroquinolones in *Escherichia coli* and *Neisseria gonorrhoea*, they have increased.^{14,15} In hospitals there is also growth in MRSA as a proportion of *Staphylococcus aureus* isolates.¹³

In a UK study carried out between 1 May 1997 and 31 March 2002, information was collected on almost three million patients in 102 participating hospitals to examine the causes and distribution of bacteraemias and the prevalence of microbial resistance. Complete data showed that there were 10,871 episodes of bacteraemia in 10,300 patients. Overall, 3.5 patients per 1,000 admissions

Dr Cooke is chairman of the prescribing subgroup of the Department of Health Specialist Advisory Committee on Antimicrobial Resistance (SACAR) and is director of research and development and chief pharmacist at the South Manchester University Hospitals NHSTrust, Manchester (email: jonathan.cooke@smuht.nwest.nhs.uk)

developed bacteraemia, and the mean bacteraemia rate was 0.6 bacteraemias per 1,000 patient-days.

There was a wide variation in rates of hospital-acquired bacteraemia between specialities. The highest rates occurred in general, paediatric and neonatal intensive care units (ICUs), and haematology. General medicine, general surgery, general ICU, haematology, and geriatric medicine accounted for 71 per cent of all bacteraemias. Almost two-thirds of bacteraemias of known source were associated with an intravascular device or with device-related infections, such as a catheter-associated urinary tract or ventilator-associated respiratory tract infection. Central intravenous catheters were the most common source of hospital-acquired bacteraemia.

Over 40 per cent of the isolates causing hospital-acquired bacteraemia were staphylococci (26 per cent *Staphylococcus aureus* and 16 per cent coagulase-negative staphylococci) and 10 per cent of all hospital-acquired bacteraemias were caused by more than one organism. Over half of *Staphylococcus aureus* were resistant to methicillin (ie, were MRSA). There was no evidence of vancomycin-resistant *Staphylococcus aureus*.

Overall, 7 per cent of all enterococci were resistant to vancomycin. However, resistance to vancomycin varied from 3 per cent for *Enterococcus faecalis* to 17 per cent for *Enterococcus faecium*.¹⁶

There are also reports of new and potentially life threatening isolates being identified in the UK. These include vancomycin-intermediate *Staphylococcus aureus*, Enterobacteriaceae that have CTX-M- β -lactamases (extended-spectrum β -lactamases [ESBLs] that are active against cefotaxime)¹⁷ and *Pseudomonas* and *Acinetobacter* spp with metallo-carbapenemases.¹⁸

SOURCE OF NEW ANTIBIOTICS

Safety, efficacy and cost-effectiveness will determine the place of a new antibiotic in clinical practice. The changing patterns of resistance in both primary and secondary care will create a need for newer agents. However the cost of bringing a new antibiotic to market is considerable, estimated to be between \$US500m and \$US1bn (£300–550m) (personal communication, McMahon C).^{2,19,20} The high costs are due to the fact that only 10 per cent of new agents which start phase I studies get to market.

Although there are a number of interesting new compounds in the antibacterial pipeline (see Panel 2, p268), it is considered that few of them are likely to reach blockbuster status. It appears that most industry activity seems to be focused on second-generation compounds, or the reformulation of existing products for new patient groups or therapeutic uses. Analysis of the antibacterials pipeline has revealed a relatively small number of new experimental antibiotics. Of these, only a few are undergoing late-stage clinical evaluation with even fewer expected to reach the market. It is interesting to note that current antibacterial market leaders, particularly those in western markets, have relatively little involvement as most are reducing their investment in this field and leaving most innovation to Japanese based firms and other smaller companies.

NEW ANTIBIOTIC AGENTS

Daptomycin In September 2003 the US Food and Drug Administration (FDA) announced the approval of daptomycin injection for the treatment of complicated skin and skin structure infections caused by *Staphylococcus aureus* (including MRSA), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subspecies equisimilis and *Enterococcus faecalis* (vancomycin-susceptible strains only). Daptomycin is the first approved product in a new class of antibiotics called cyclic lipopeptide antibacterial agents and treats infections in a way that is distinct from any other antibiotic. It binds to bacterial cell membranes causing rapid depolarisation, inhibiting the synthesis of DNA, RNA and proteins. The most common adverse events include gastrointestinal disorders, injection site reactions, fever, headache, insomnia, dizziness and rash. Patients receiving daptomycin should be monitored for the development of muscle pain or weakness and creatine phosphokinase (CPK) levels should be monitored weekly. Those who develop unexplained elevations in CPK while on daptomycin should be monitored more frequently.²¹

A Marketing Authorisation Application is to be submitted to the European Medicines Agency (EMA) for daptomycin injection, as a once daily treatment for complicated skin and soft tissue infections caused by Gram-positive bacteria, including MRSA.

Tigecycline Tigecycline is a novel glycylicline antibiotic that is an analogue of the

semi-synthetic tetracycline, minocycline. It has been developed as an agent that can overcome tetracycline resistance mechanisms and have an activity against multidrug resistant organisms.

The *in vitro* activity of tigecycline was reported using a worldwide collection of over 10,000 Gram-positive bacteria. The organisms tested included both methicillin sensitive and resistant *Staphylococcus aureus*, coagulase negative staphylococci, pneumococci, both penicillin sensitive and resistant enterococci, both sensitive and resistant to vancomycin *Viridans streptococci* and lastly the β -haemolytic streptococci.

Tigecycline was uniformly active against methicillin sensitive *Staphylococcus aureus* (MSSA), MRSA and the coagulase negative staphylococci. All the enteric bacteria except for one strain of *Proteus mirabilis* were deemed to be sensitive to tigecycline. Tigecycline, however, has no effect against pseudomonas. Similarly a further report showed that tigecycline was also active against *Haemophilus influenzae*, *Moraxella catarrhalis* and *Neisseria meningitidis* and therefore may have a role to play in respiratory tract infections and meningitis.²²

Dalbavancin Dalbavancin is a novel semisynthetic glycopeptide with enhanced activity against Gram-positive species. Dalbavancin exhibited excellent activity against Gram-positive strains tested.²³

Telithromycin Results from two studies presented at the American Lung Association and the American Thoracic Society conference suggested that once daily telithromycin treatment for five or seven days in patients with community-acquired pneumonia, or five days in patients with acute exacerbations of chronic bronchitis was as active as commonly used antibiotics taken two or three times a day for 10 days.²⁴

Peptide deformylase inhibitors The activities of six peptide deformylase (PDF) inhibitors against 107 respiratory tract pathogens were studied and compared with those of ciprofloxacin and amoxicillin-clavulanate. PDF is an enzyme which is essential and unique to bacteria. Against *Streptococcus pneumoniae*, BB-83698 and BB-83815 were the most active PDF inhibitors. Five of the agents showed similar activity against *Moraxella catarrhalis*. All PDF inhibitors were less active against *Haemophilus influenzae*; BB-3497 was the most active agent. Five agents were studied against *Chlamydia* spp and showed activity similar to that of ciprofloxacin. This study demonstrates that PDF inhibitors have the potential to be developed for the treatment of respiratory tract infections.²⁵

Non-antibiotic developments Vaccines are becoming available for the treatment of certain infections that previously had been difficult to treat. For example Prevenar (Wyeth), a protein-conjugated pneumococcal vaccine, has been developed for active immunisation of infants and young children from two months

Panel 1: Numbers of antimicrobials listed in the BNF

	1968	1978	1988	1991	2004
Penicillins	6	10	25	28	10
Cephalosporins	4	14	14	14	13
Aminoglycosides	4	4	7	7	5
Others	15	14	33	35	34
Total	29	42	79	84	62

to two years against invasive disease caused by a number of serotypes of *Streptococcus pneumoniae*. Similarly StaphVAX, a vaccine directed against *Staphylococcus aureus* is active against strains that are responsible for 80–90 per cent of clinical infections caused by this organism.

Bacterial genome sequencing Potential new areas for the treatment of infectious diseases might be seen with identification of bacterial genomes.²⁶ Since the first genome was identified in 1995 there are now 100 different bacterial genomes available. New agents might be expected to be developed eventually through this programme.²⁷

Other antimicrobial agents Other novel agents such as Fab-I and Fab-K (enzymes involved in bacterial fatty acid biosynthesis) directed antibacterials offer potential therapeutic options for the treatment of multidrug resistant organisms.²⁸

CONCLUSION

Whether all these new agents will help in the fight against resistance is a matter of some debate. More work needs to be done on the effectiveness of formularies and guidelines and cycling strategies or the use of short intensive courses. Until the results of these are determined it seems prudent to continue to focus on the rational and informed selection and use of these agents.

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Panel 2: New antimicrobial agents expected to emerge on to world markets in the next six years (communication, K Coleman)

Agent	Class	Company	Route	Launch
Daptomycin	Cyclic lipopeptides	Cubist	iv	2004
Doripenem	Carbapenem	Shionogi	iv	2004
Doripenem inhaled	Carbapenem	Peninsula	inhaled	2006
R 115685	Carbapenem	Sankyo/Roche	iv	2010
Tebipenem	Carbapenem	Meiji Seika	po	2007
BAL 5788	Cephalosporin	Basilea	po	NK
CB 181963	Cephalosporin	Cubist	iv	2010
RWJ 442831	Cephalosporin	J&J	po	NK
RWJ 54428	Cephalosporin	J&J	iv	NK
S3578	Cephalosporin	Shionogi	iv	2010
Iclaprim	Diaminopyrimidine	Arpida	iv	NK
Dalbavancin	Glycopeptide	Vicuron	iv	2005
Oritavancin	Glycopeptide	InterMune	iv	2005
TD 6424	Glycopeptide	Theravance	iv	2004
Telithromycin	Macrolide	NK	NK	NK
Cethromycin	Macrolide	Taisho	po	2007
Ranbezolid	Oxazolidinone	Ranbaxy	NK	NK
BB 83698	PDF inhibitor	GTC	po	NK
LBM 415	PDF inhibitor	Novartis/Vicuron	po	NK
DX 619	Quinolone	Daichi	po/iv	NK
Garenoxacin	Quinolone	Toyama/Schering	po/iv	2006
WCK 771	Quinolone	Wockhardt	iv	NK
PTK 0796	Tetracycline	Bayer/Paratek	iv	NK
Tigecycline	Tetracycline	Wyeth/Ayerst	iv	2004
Quillimmune-P	Vaccine	Antigenics	NK	2006
StaphVax	Vaccine	Nabi	NK	2005

NK: Not known, iv: intravenous, po: oral

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