registration by both the European Medicines Agency and the Food and Drug Administration, and approval from the National Institute for Health and Clinical Excellence for its use in defined clinical settings.[14,15] Nevertheless, the lack of a second confirmatory clinical trial and the failure of the ADDRESS study in lower-risk patients means that many intensivists remain uncertain about the precise role of this drug.[16]

What is encouraging – and in some senses surprising, given the difficulty in making headway in this field – is that novel agents continue to come forward from the basic science arena. For instance, there is currently much interest in the possibility that Toll like receptors (in particular TLR4) may be good therapeutic targets and two large clinical trials of small molecule antagonists have begun.[17,18] What is clear is that driving down the mortality in this condition remains a major unmet medical need.

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Antimicrobials: past, present and uncertain future

Roger Finch, *Professor of Infectious Diseases, School of Molecular Medical Sciences, University of Nottingham*

Email: R.Finch@nottingham.ac.uk

It is hard to imagine the practice of medicine without antibiotics. Life-threatening infections, such as meningitis, endocarditis, bacteraemic pneumonia and puerperal sepsis, would again prove fatal. Minor community-managed infections would be associated with slower recovery, higher complication and hospital admission rates, while surgical practice would see steep rises in postoperative infectious complications. Aggressive chemotherapy and transplant procedures would prove impossible.

Why create this scenario? Antibiotics are unique among therapeutic agents. Although prescribed for diseases, syndromes and symptom complexes, they target pathogenic organisms rather than an intrinsic host-derived pathophysiological process. Furthermore, their efficacy is eroded as resistance emerges and disseminates. There is therefore a requirement for surveillance of resistance, encouragement of prudent prescribing and observance of practices that reduce the risk of resistant pathogens emerging or disseminating. Continuous technological innovation is essential to ensure an adequate flow of new drugs, vaccines and diagnostics to manage existing and emerging infections. Currently this process is in a state of imbalance.

The dominance of β-lactam antibiotics (penicillins and cephalosporins) emphasises the fundamental importance of Fleming's discovery of penicillin and the landmark identification of the 6-aminopenicillanic acid nucleus by Rolinson and colleagues which presaged structure-based drug design.[1,2] The legacy is remarkable and includes the aminopenicillins (eg amoxicillin), the isoxazolyl penicillins (eg meticillin, flucloxacillin) and the piperazinyl penicillins (eg piperacillin). This laid the technical know-how for the development of the cephalosporins whose derivatives have proved the work horse antibiotics in hospital and community practice for four decades. Currently, the elusive target of a cephalosporin active against methicillin-resistant *Staphylococcus aureus* (MRSA) appears in site with the trialling and imminent licensing of ceftibiprole.

Antimicrobial science has proved innovative not only in discovering new compounds but in defining the myriad and ever-increasing mechanisms of microbial resistance. Enzymatic

inactivation is common, but in the case of β-lactamases, has in part been countered by inhibitors, such as clavulanic acid, sulbactam and tazobactam. Target site modification, resulting from *erm* gene mutations has encouraged the development of new macrolides such as telithromycin (strictly a ketolide), while recent fluoroquinolones (eg moxifloxacin) inhibit both subunits of DNA gyrase and topoisomerase IV. Unfortunately, this latter development has probably come too late to have any significant impact on current resistance trends to fluoroquinolones which are now also vulnerable to plasmid-mediated resistance.[3] Less successful have been attempts to develop inhibitors of efflux pumps which act by extruding antibiotics from the microbial cell and which are widespread in Gram-negative pathogens.[4]

In clinical trials, the most important determinant of efficacy and safety is to define the dosage regimen and optimum duration of treatment. However, this remains a huge challenge on account of variables such as age, excretory organ function, possible drug interactions and endpoints (microbiological and clinical) which are often difficult to determine, or require financially prohibitive large studies.

The dynamic relationship between drug, pathogen and host has been intensively studied, modelled and applied to drug development and therapeutics. The relationship between the pharmacokinetic profile of a drug and its pharmacodynamic effects on the target pathogen is now fundamental to new drug development.[5] It can identify dose magnitude and frequency of administration in relation to predicted and measured efficacy for target infections, such as pneumonia, urinary tract and cutaneous infections.[6] It is also being exploited to determine drug concentration least likely to induce resistant mutants.[7]

What of the future? Currently, there is a mismatch between investment in new antibacterial drug development and the attrition of existing agents as a result of resistance. Despite the fact that the genome structure is known for more than 35 human pathogens, no genomic-based agent has yet been licensed. Only two new classes of agent have been developed in the past 30 years, oxazolidinones (linezolid) and lipopeptides (daptomycin). While several new agents are under development, too few are truly novel compounds. Much effort has been put into developing agents active against Gram-positive pathogens, notably MRSA and *Streptococcus pneumoniae* (eg telavancin, oritavancin, dalbavancin and iclaprim). However, resistance to β-lactam antibiotics and other agents among many common Gram-negatives, such as *Escherichia coli, Klebsiella* spp and *Pseudomonas aeruginosa* is increasing, not only in hospital but also in the community, while some new agents are available (eg tigecycline), new pathogens, such as *Acinetobacter* spp are causing epidemics and for which recourse to obsolete and toxic agents, such as colistin, has proved necessary. Drug discovery is increasingly looking to academic and small biotechnology-based laboratories for solutions.[8] Some excitement has been generated by the discovery of small naturally occurring and synthetic peptides with antimicrobial activity eg the megainins.[9] Likewise, the recognition that micro-organisms generate a number of quorum sensing or signal molecules which permit cell-to-cell communication both *in vitro* and *in vitro* has led to a search for signal pathway blockers.[10]

The obstacles to new drug development are not just technological, but include the way anti-infective agents are viewed and used by healthcare systems. Their very success has led to overuse and inappropriate use. The goal of improving prescribing practice has been linked to efforts in cost containment through generic use. High-cost agents are often reserved for difficult or resistant infections. The wisdom of this strategy should be reviewed as resistance increases, since industry is unlikely to develop new products without a market. To maintain an adequate flow of new agents will require a greater acceptance that a higher price for new therapies may be prudent in the longer term. Furthermore, current policies that encourage the reclassification of drugs from prescription only medicines to those available through pharmacy provision need careful review to ensure that they are not working counter to public health efforts to control antimicrobial resistance.[11]

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