

for the pound?" At least, that is what they should ask if they desire an NHS that can keep them healthy and safe at an affordable price for as long as is feasible.

Donald M Berwick *president*

Institute for Healthcare Improvement, 20 University Road, Cambridge MA 02138, USA
(dberwick@ihi.org)

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Treatment of staphylococcal infection

Prescriptions must be part of a package that includes infection control

We have seen a spectacular rise in multiresistant *Staphylococcus aureus* (usually termed methicillin resistant *Staphylococcus aureus*—MRSA) in hospitals and care homes in the United Kingdom in the past five years.¹ The emergence and spread of modern resistant bacteria are not simply the result of mutations or gene transfer in the diverse species we call *S aureus*,² as occurred when resistance first developed.³ Instead the resistance is now spread by the dissemination of a tiny number of clones, which have a predisposition towards resistance and have been selected by current treatment. So how does one treat staphylococcal infection?

In particular, two clones, epidemic MRSA (EMRSA)-15 and EMRSA-16, account for more than 95% of MRSA strains isolated in the United Kingdom.⁴ The carriage of resistance in these bacteria seems to be associated with no fitness cost—the acquisition of resistance does not slow the growth of the bacteria and thus put them at a selective disadvantage once the antibiotic is removed.⁵ So now the prescriber is faced with a different problem, the widespread dissemination of a limited number of virulent MRSA types. These can persist for long periods and have a predisposition to acquire further resistance genes readily, which could mean that these resistant clonal strains will become pan-resistant and completely untreatable with antibiotics.

When considering treatment options, prescribers have two responsibilities. The first and most immediate is to the patient. For the patient, the most effective treatment is the best choice. However, this consideration alone has not stemmed the rise in resistance. So prescribers also have to consider the impact of the antibiotic on the levels of resistant bacteria. Development of resistance is a two stage process. The first stage is the initial emergence of resistant strains, and the next is their dissemination. The first stage could occur in a non-clinical situation, such as during animal husbandry.⁶ This is possible but unlikely. Once resistance has become established, even low drug usage can maintain it or even increase its spread in the population. Most antibiotic prescribing facilitates the dissemination of clonal resistant bacteria, and this is where precautions need to be planned carefully.

If we consider MRSA in the United Kingdom, we find strains that are highly resistant to all but a few antibiotics, which generally include the glycopeptides. So the glycopeptides vancomycin and teicoplanin may still be used cautiously. This means prescribers should be aware that intermediate resistance to vancomycin has been reported,⁷ they should find out if resistance has been reported in their immediate area, and also keep in mind that these resistant bacteria would be encouraged and their numbers increased by individual prescription of these drugs. Clinical resistance to high concentrations of glycopeptides has emerged by transfer of the *vanA* operon from vancomycin resistant enterococci into MRSA in the United States.⁸ Therefore, vancomycin resistant MRSA now only has to disseminate, and every prescription for glycopeptides will support this. So the choice to prescribe a glycopeptide must be based on the local risk of favouring the spread of glycopeptide resistant clones.

What are the alternatives? These are not found in our usual armamentarium but with the oxolinidones, daptomycin, and streptogramins. These drugs can be effective in certain situations but are unlikely to become the universal panacea for the treatment of staphylococcal infections. The US Veterans Health Administration recommends that these drugs should generally be reserved for serious infections for which no alternative antimicrobial treatment exists.⁹ It says that any of these drugs could be used for complicated infections of the skin or skin structure and one or more of the following—proved resistance to vancomycin; infection in patients who do not tolerate vancomycin because of allergy or serious adverse drug reaction; and failed treatment with vancomycin. It also says that oral linezolid can be used only in patients suitable for oral treatment for whom treatment with oral trimethoprim-sulfamethoxazole, tetracyclines, fluoroquinolones, and clindamycin is inappropriate because of microbial resistance or intolerance of these medications. It further recommends only linezolid for the treatment of staphylococcal pneumonia but warns of the risk of linezolid resistance and highlights the fact that the US Food and Drug Administration does not recommend the use of any of these drugs for the treatment of endocarditis or bone and joint infections.

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Resistance to multiple antibiotics in *S aureus* is a problem that all prescribers should consider if we are to preserve our capability to treat infections. However, we need to understand that what we are trying to control is the spread of the bacteria, which are already resistant to most antibiotics, rather than the initial emergence of resistance. With that in mind, prescription must be part of a package that includes infection control and the implementation of hygiene barriers that prevent the cross infection of patients. Only then would we have any prospect to reduce resistance sufficiently to allow us to reintroduce the antibiotics we used earlier.¹⁰ We also need to remember that antibiotic treatment for Gram positive bacteria is often less effective at controlling Gram negative bacteria. Some strains are pan-resistant and are now at least as difficult to control as MRSA, and it would be ironical if we defer one problem only to have to confront a worse one.

Sebastian G B Amyes *professor of microbial chemotherapy*

Medical Microbiology, Centre for Infectious Diseases, Medical School, University of Edinburgh, Edinburgh EH8 9AG (s.g.b.amyes@ed.ac.uk)

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Surveying the literature from animal experiments

Critical reviews may be helpful—not systematic ones

The value of animal research for finding new treatments for human diseases is a continuing debate. The starting point of the debate must be the recognition of the past contributions of animal experiments to our understanding of disease and existing treatments. We can cite the major impact of research based on animals in diseases such as polio, kidney transplantation, and Parkinson's disease. Almost every form of conventional medical treatment (including most drugs, surgical treatments, and vaccines) was developed with the help of animal research.¹⁻³ Most of what we know about the basic workings of the body—in humans and animals—has come to us through two centuries of animal experiments. Each decade of animal research has brought newer and deeper understanding.⁴ What we lack, however, are better methods of surveying the literature on animal experiments.

Curiosity about fundamental biological mechanisms has yielded a rich harvest of useful knowledge. Although around 30% of current animal research is categorised as “fundamental” by the Home Office,³ much of this targets specific diseases. How do we know when the information gained from animal experiments is strictly relevant for the planning of clinical trials of new drugs?

It might seem straightforward to ensure that, before a clinical trial of a new treatment commences, all relevant results from animal studies are systematically reviewed for evidence of safety and efficacy. Perhaps the best known case is that of the calcium channel blocker nimodipine as a potential neuroprotective agent after stroke. Some authors have claimed that animal experiments failed to prevent the problems that occurred in the clinical trials.^{5,6} But ani-

mal experiments did reveal the deleterious effects of this drug, and these results were published. The clinical trials, however, went ahead despite evidence from animal experiments that suggested caution. Why? What are the pressures (scientific, commercial, and others) that allow trials to progress even when the evidence is not compelling or even ambiguous? And what are the requirements to weigh all available evidence in balance rather than select the data that support the personal or economic imperative? Although the example of nimodipine is well known, other powerful recent examples of animal research informing medical advance also exist—for example, the recent development of a vaccine for the severe acute respiratory syndrome.⁷

We need better methods of surveying the literature on animal experiments. The huge year on year increase in the numbers of studies reported makes it ever more likely that vital pieces of evidence go undetected. However, the proposal that systematic reviews of animal based research might solve this problem has two fundamental problems. Firstly, no mechanism exists for so called negative results to be published. Thus the absence of evidence for a particular drug action must often be inferred. This is not just an issue of publication bias; it is intrinsic to the experimental process. Scientific experiments are designed to test for evidence in favour of a particular experimental hypothesis and to abandon it if insufficient evidence is acquired.

Secondly, the style of clinical trials and of animal research have important generic differences. Clinical trials of putative treatments entail testing the treatment on a cohort of sick humans. The design can vary, but the subjects can be quite similar from one trial to