ARE WE RUNNING OUT OF ANTIBIOTICS?

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Resistance amongst bacteria predates antibiotic use in humans. Collections of bacteria established for taxonomic purposes before the clinical use of antibiotics contain organisms resistant to antibiotics. This is to be expected when one remembers that many soil and other bacteria excrete bactericidal substances, bacteriocins, into their environment to ensure their own survival amongst millions of competing organisms.

Since antibiotics have been in widespread clinical use, resistance has become commonplace. By 1950 infection with penicillin-resistant *Staphylococcus aureus* had become a widespread problem in hospital patients. This subsequently spread into the general community, so that now only about 10% of *S. aureus* isolates from community patients are susceptible to penicillin. Methicillin resistance is appearing in Westem Australian isolates of *S. aureus,* ten years after methicillin resistance became widespread in the eastern States. Similarly, virtually all *Klebsiella* species isolated from the Western Australian population were susceptible to ampicillin in the 1950s, but are now all resistant. This resistance has spread into approximately 55% of all *Escherichia coli* and many of the other enterobacteriaceae.

Penicillin resistance is well known in *Neisseria gonorrhoeae* and has now been found in *Neisseria meningitidis* (none reported in Australia as yet). Penicillin resistance is becoming increasingly common in Australian isolates of *Streptococcus pneumonia*e, and invasive pneumococcal infections such as meningitis, which cannot be treated with penicillin, are being encountered. At present resistance to third-generation cephalosporins is rare and patients with pneumococcal meningitis should be treated with ceftriaxone or cefotaxime at least until susceptibility to penicillin has been confirmed in the laboratory.

How antibiotics work

Antibiotics in low concentrations are selectively more toxic to bacteria than they are to humans. In order to be effective, the organisms must be susceptible to an achievable concentration of the antibiotic. The most succesful compounds appear to be those that interfere with the construction of the bacterial cell wall, the synthesis of protein on the bacterial ribosome or replication and transcription ot bacterial DNA. Very few clinically useful agents act at the level of the cell membrane or by interfering with specific metabolic processes.

Mechanisms of antibiotic resistance

These include:

(1) inactivation of the antibiotic before or after entering the bacterial cell. Examples include the many beta-lactamases produced by *S. aureus* and many Gram-negative enteric bacteria;

(2) alteration of the cell surface to become less permeable to the antibiotic; and

(3) modification of the antibacterial target structure so that it cannot bind to the antibiotic.

Bacteria achieve these apparently simple goals in a bewildering variety of ways, some (probably many) of which still await discovery. For example there are at best 44 different beta-lactamases produced by Gram-negative enteric bacteria; of these, about nine are quite common, and 27 are rare.

Bacterial resistance to a particular antibiotic may be 'constitutive', that is, no member of the species or genus is susceptible to the antibiotic in question because they lack the target required by the antibiotic; this is usually chromosomally specified.

Antibiotic resistance may also be acquired. This may be due to:

(1) *Mutation in the bacterial chromosome* resulting in a gene product with reduced or absent ability to bind the antibiotic. Examples include high-level resistance to streptomycin in *M. tuberculosis,* penicillin-resistant *S. pneumoniae,* penicillin-resistant *N. gonorrhoeae,* and fluoroquinolone-resistant *E. coli;*

(2) *Acquisition of resistance genes via plasmids.* Plasmids are self-replicating molecules of DNA which exist in the bacterial cell cytoplasm, and which usually produce a drug-inactivating or drug-modifying enzyme. Large plasmids often code for resistance to several antibiotics. Plasmids are most commonly transferred by conjugation between bacterial cells, and are common amongst Gram-negative enteric bacteria. In the laboratory, plasmids may also be transferred via bacteriophages, and also by transformation (uptake of naked DNA which has been released into the bacterial cell's environment), but it is not known how often this occurs in nature.

(3) *Acquisition of resistance genes via transposons.* Transposons are discrete DNA sequences which transfer and rearrange their genetic material (encoding for resistance to a wide variety of antibiotics as well as many other metabolic properties) between bacterial chromosomes and/or plasmids. They are responsible for much of the development and spread of antibiotic resistance in hospitals. Once integrated into the host bacterium's chromosome, transposons are spread as stable genetic elements.

Transfer of resistance between disparate bacterial genera

When antibiotics are used, resistant bacteria are rapidly selected and become dominant amongst the patient's normal flora. This is particularly the case if the patient being treated is exposed to the bacterial flora of many other people, as occurs in hospital (this is fairly obvious with toddlers, but also occurs with adults.) Thus the best way of conserving antibiotics is not to use them. Unfortunately even if this were practical, once resistance to a new antibiotic has developed it can spread worldwide within two or three years.

Information on the types and modes of transfer of antibiotic resistance within and between bacterial species and genera is still expanding. Interesting examples include the identical erythromycin resistance genes found both in some *Streptococci* (Gram-positive) and also in some *Campylobacter* species (Gram-negative), and the acquisition by enterococci of aminoglycoside and beta-lactam resistance from *Staphylococci.* Although many resistance mechanisms remain unknown, clinical experience has shown that the mere use of antibiotics is a powerful selection factor for antibiotic-resistant organisms.

Responsible use of antibiotics

While we are aware of increasing antibiotic resistance in Australia and other countries with good controls on the supply of antibiotics, it is a much greater problem in countries such as Spain, where drugs can be freely purchased without a medical prescription. Thus controls must be in place to ensure that antibiotics are used only when necessary. Antibiotics are also used widely in agriculture to maximise meat and egg production, but current opinion is divided about the effect of this practice on the spread of antibiotic resistance amongst the human population. This would undoubtedly be a major influence if meat were eaten without cooking, but when it is cooked adequately (and stored separately from uncooked meat after cooking) most bacteria are killed.

What else can be done to preserve antibiotics for future use?

Advocated measures include:

Prevention of infection wherever possible. This includes improvement of living standards for people living in poor conditions, such as Australian Aborigines, and the universal use of the effective vaccines currently available.

Early and accurate clinical diagnosis. Laboratory diagnosis of the pathogen depends upon appropriate specimen collection. Adequate samples, preferably from ordinarily sterile sites, provide the best chance of identifying the true pathogen(s).

Rapid laboratory identification of antibiotic resistance is essential, and may be quite difficult for some types of bacteria.

Laboratory surveillance of antibiotic susceptibility patterns of local strains of bacteria is important to enable reliable antibiotic selection for individual cases before laboratory results are available, to document changes at both local and national levels, and to provide an early warning of cross infection problems.

Selective reporting of antibiotic susceptibility is recommended.

Early and appropriate treatment, including surgical drainage of pus and debridement of necrotic tissue is essential in order to reduce the infective load. Patients can still die despite being given appropriate antibiotics if surgery is unduly delayed.

Choice of antibiotic may vary with the type of patient, as well as the type of infection, thus

Narrow spectrum antibiotics should be given wherever possible.

Broad spectrum treatment may be required for immunocompromised patients more ofen than for previously healthy adults. In this context the compromised include patients at the extremes of age, pregnant women, those with chronic or severe underlying illness, as well as those with primary or acquired immunodeficiency.

Broad spectrum antibiotics may also be indicated in mixed or unknown infections rather than using combinations of drugs, or to avoid toxicity (e.g. aminoglycoside).

Antibiotic combinations may be indicated where -

(1) the pathogen is unknown, but could be one or more of several bacteria;

(2) infection is mixed;

(3) antibiotic synergy is required, such as in the treatment of endocarditis;

(4) drug resistance must be prevented, such as in mycobacterial infection;

(5) reduced dosage of toxic agents can be achieved such as therapy of *Candida* infections with amphotericin and 5-fluorocytosine.

The site of infection is critical for it is here that adequate antibiotic levels must be achieved. Thus dosage, mode of administration, and choice of antibiotic often vary with the type and location of infection. Antibiotic levels at the site of infection must be at least equal to or greater than the minimal inhibitory concentration (MIC) of the organism. Thus intracellular organisms such as *Salmonella typhi* best respond to an antibiotic that penetrates cells (eg. ciprofloxacin).

Adjuvant therapy may affect antibiotic levels present at the site of infection: dexamethasone given for meningitis decreases penetration of vancomycin into the CSF, reducing its effectiveness in the treatment of penicillin resistant pneumococcal infection.

Host response to infection may necessitate different levels of dosage or choice of antibiotics. For example fever may recur in pneumococcal meningitis as the blood-brain barrier is restored, reducing the penetration of penicillin into the CSF; this can be corrected by doubling the dose of intravenous penicillin G.

Duration of treatment varies with the type of infection. For most conditions the optimum duration of antibiotic treatment has not been scientifically defined, often varies with host factors and therefore depends upon clinical judgement. For this reason frequent clinical review is necessary.

Antibiotics used for *surgical prophylaxis must 'cover' the usual normal flora for the operative site* and be given for the minimum time, which is usually a single dose. If surgery is prolonged a second dose may be given in order to maintain therapeutic tissue levels for up to six hours afterwards.

Infection control measures to identify and correct cross infection problems are integral to reducing spread of antibiotic resistant organisms. Apparently insignificant or unrecognised changes in hospital standards may lead to major opportunities for selection of 'new' pathogens; thus if pan-flusher sanitising equipment fails to reach adequate operating temperatures antibiotic resistant enterococci can survive and cause nosocomial infections.

Clinical pharmacists have an important role to play in identifying patients whose antibiotic regimens may require adjustment. Not only are the latest broad-spectrum antibiotics often very expensive, but if used indiscriminately and without justifcation, their useful life will be shortened. Automatic stop-orders and criteria for prescription of these drugs are likety to become more common in future.

Principles for conservation of antibiotics

The principles incorporated in the above guidelines were devised by Jawetz almost 50 years ago, but are often overlooked. In summary they comprise adherence to stringent policies to reserve the use of antibiotics for appropriate indications and duration of therapy, continuing nationwide and hospital surveillance for antibiotic resistance (for developing and modifying antibiotic policies as appropnate) and development of and adherence to appropriate infection control policies to reduce nosocomial spread of antibiotic-resistant organims. These measures, together with rapid diagnostic tests to identify pathogens, have stood the test of time. They must be remembered, as today they offer us our best chance of extending the useful life of existing antibiotic agents.

Further reading: Chin G J, Marx J (eds). Resistance to Antibiotics. *Science* 1994;264:359-393.