Focus

Antibiotic resistance and the GP: when less is more

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Antibiotic resistance is a topical subject. There is worldwide concern that, unless action is taken by the profession to reduce antibiotic prescribing, we may soon be unable to treat some commonly presenting infections in both general and hospital practice. This article gives some background on the topic and suggests strategies for dealing with the problem, particularly with respect to respiratory infections.

Key points

- Antibiotic resistance in common pathogens is increasing, especially with respect to S. pneumoniae
- No new classes of antibiotic are on the horizon
- Good overseas evidence shows that inappropriate (and appropriate) antibiotic prescribing drives the development of resistance
- Antibiotic use in viral infections is not only ineffective but also potentially harmful
- When antibiotics are taken for viral infections they always act on the commensal flora and select out the resistant strains
- Children who have recently had antibiotics are two to seven times more likely to subsequently carry resistant strains of S. pneumoniae as commensals

History

Apart from simple analgesics, antibiotics are the most commonly prescribed of all drugs. The first antibiotic introduced was a sulphonamide, Prontosil, in 1932, but it was the introduction of penicillin in 1944 that marked a turning point in the history of modern medicine. Pneumonia, septicaemia, TB, meningitis and infections after childbirth and abdominal surgery were often fatal before antibiotics. Now they are successfully treated almost as routine.

However, no new major class of antibiotic has been introduced in the last 15 years. The 1980s and 1990s yielded only improvements within classes, such as the addition of clavulanic acid to amoxycillin to combat beta-lactamase enzymes. It is unlikely that any new class of antibiotic will be introduced in the next decade. As we approach the new millennium, bacteria are gaining ground and people are beginning to die from infections resistant to every known antibiotic.

Development of resistance

Resistance to antibiotics began to be noted soon after they were first introduced. Because bacteria multiply so rapidly, they have an incredible capacity to develop resistance. Live cells can take up DNA released by dead cells. Genetic material can be exchanged between bacteria by viruses (called bacteriophages). Resistance genes are commonly carried on tiny loops of DNA called plasmids. Bacteria can transfer these plasmids not only among their own type, but also to different species.

Genes for antibiotic resistance are often present on the

same plasmid, so resistance to two or more antibiotics can be transferred simultaneously. The exchange of genes is so pervasive that the entire bacterial world can be thought of as one huge multicellular organism in which the cells interchange their genes with ease.

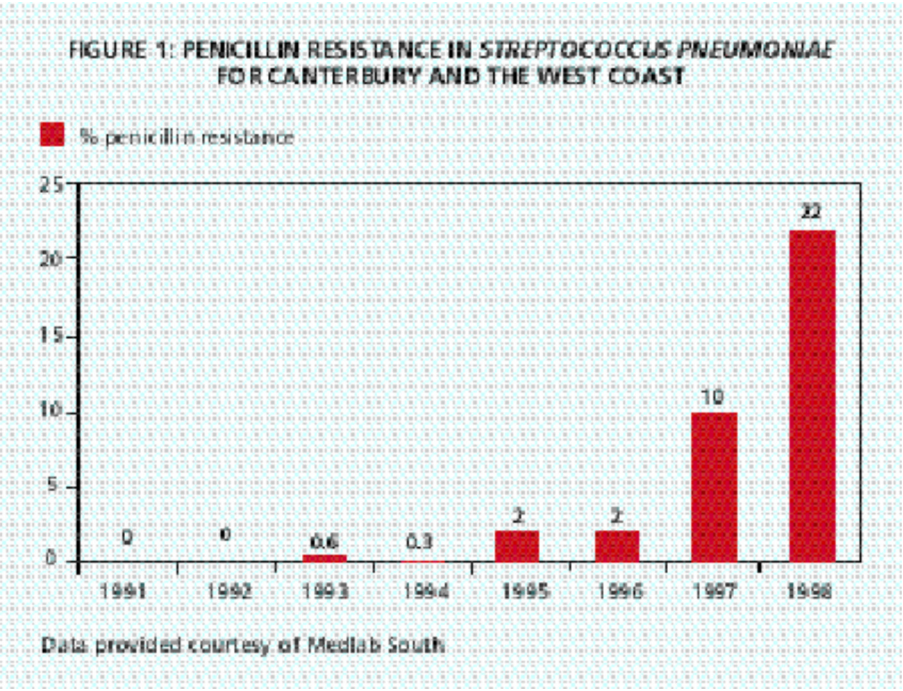
- Among patients with invasive disease due to S. pneumoniae, recent antibiotic use has been identified as a risk factor for infection with strains resistant to multiple drugs

Natural selection plays a large role. When an antibiotic is given against a population of bacteria, cells that are highly susceptible will die. But cells that have some resistance from the start, or acquire it later through mutation or gene exchange, may survive. These cells, facing reduced competition from susceptible bacteria, will go on to proliferate.

When resistant bacteria arise in a treated individual they can spread readily to new hosts. So antibiotic resistance that develops in one place can spread far and wide, within communities and internationally, provided the selective pressure of antibiotic prescribing is maintained.

However, in the absence of antibiotics, susceptible strains have a slight survival advantage because the resistant bacteria have to divert some of their valuable energy from reproduction to maintaining antibiotic-fighting traits. Ultimately the susceptible microbes will win out.[1]

By reducing the amount of antibiotic prescribed we can hope to reduce the level of antibiotic resistance. This has been achieved in Finland, where reduced prescribing of macrolides lowered the percentage of Group A *Streptococcus pyogenes* resistant to erythromycin from 16.5 per cent in 1992 to 8.6 per cent in 1996.[2]



In Iceland, penicillin resistance in *S. pneumoniae* increased rapidly from 2.3 per cent in 1989 to 20 per cent in 1993. Reduced antibiotic prescribing between 1992 and 1995 was able to halt the rapid increase in resistance. By 1994 the incidence had declined to 16.9 per cent.[3]

Difficult to treat bacteria

Some isolates of three bacterial species (*Enterococcus faecalis, Mycobacterium tuberculosis* and *Pseudomonas aeru-ginosa*) have now become resistant to all known antibiotics and are essentially untreatable. Alarmingly, recent reports that some isolates of *Staphylococcus aureus* from Japan have become resistant to vancomycin signify that variants of *S. aureus* untreatable by every known antibiotic are on their

way.

Fortunately in New Zealand multi-resistant strains of *Enterococcus faecalis* and *Mycobacterium tuberculosis* are rare and not presently a concern. With respect to community acquired infections the bacteria causing most concern is *Streptococcus pneumoniae*. [4]

Streptococcus pneumoniae

This bacterium was first noted to be resistant to penicillin in the late 1960s in Australia. Since then resistant strains have been reported worldwide. Various strains of *S. pneumoniae* have also become resistant to virtually every other known antibiotic. Vancomycin is now the only antibiotic to which *S. pneumoniae* remains uniformly sensitive.

In Christchurch, penicillin resistant *S. pneumoniae* (PRSP) have increased from 0 per cent in 1992 to 22 per cent in 1998 (Figure 1).[5] Community laboratories throughout New Zealand are observing similar trends, but because these data relate to voluntary referral of specimens they cannot be taken to accurately reflect prevalence.

Penicillin works against *S. pneumoniae* by binding with certain proteins (penicillin binding proteins or PBPs) in the cell wall. Cell wall synthesis is disrupted and the cell is killed. There are at least seven different types of PBPs. Resistance to penicillin in *S. pneumoniae* is not an all-or-nothing phenomenon as is the case with, eg, *S. aureus*, which may or may not produce a beta-lactamase enzyme.

The type of alteration to PBPs and the proportion of abnormal PBPs determine the extent of penicillin resistance, which increases as a continuum. This is very relevant clinically as penicillin is still effective against even relatively resistant strains of *S. pneumoniae* providing the dose of penicillin is high enough.[6]

Many studies on *S. pneumoniae* have shown a link between the MIC (minimum inhibitory concentration) for penicillin and multiple resistance.[7] The higher the MIC for penicillin, the greater the likelihood of multiple antibiotic resistance.

Penicillin resistant strains of *S. pneumoniae* are often also resistant to cotrimoxazole, erythromycin, tetracycline and cefaclor. When a multi-resistant strain of PRSP is present in a community, treatment with any antibiotic to which it is resistant will increase the percentage of isolates resistant to penicillin.

Treatment of PRSP

Amoxycillin remains the drug of choice in general practice for treating upper and lower respiratory infections and otitis media caused by PRSP with MICs up to 2mg/l. In most situations it is still possible to achieve drug levels above the MIC. It has been shown that for amoxycillin to be effective the concentration of the drug needs to be above the MIC90 for at least 40 per cent of the time. For a "standard" 70kg adult this can be achieved with a dose of amoxycillin 500mg tid.20 It should be noted that *S.pneumoniae* is not a beta-lactamase producer so Augmentin is no more effective than amoxycillin against it.

If the strain of *S. pneumoniae* is very resistant to penicillin, ie, with a MIC >2mg/l, then less commonly used antibiotics such as chloramphenicol or a third generation cephalosporin may be required. Penicillin allergic patients present particular difficulty, as PRSP is likely to be resistant to most, if not all, other commonly used antibiotics. In these situations consultation with a clinical microbiologist or

infectious disease specialist is recommended.

In the community 30 per cent of cases of pneumonia,[8] sinusitis[9] and otitis media[10] are due to infection with *S. pneumoniae*. The highest morbidity and mortality occurs in children, especially infants, and the elderly. *S. pneumoniae* is carried in the nasopharynx as a commensal by at least 20 per cent of the population, mostly preschool children.[11]

Children who have recently had antibiotics are two to seven times more likely to subsequently carry resistant strains of *S. pneumoniae* as commensals. These resistant commensals can sometimes cause illness. Among patients with invasive disease due to *S. pneumoniae* recent antibiotic use has been identified as a risk factor for infection with strains resistant to multiple drugs.[12]

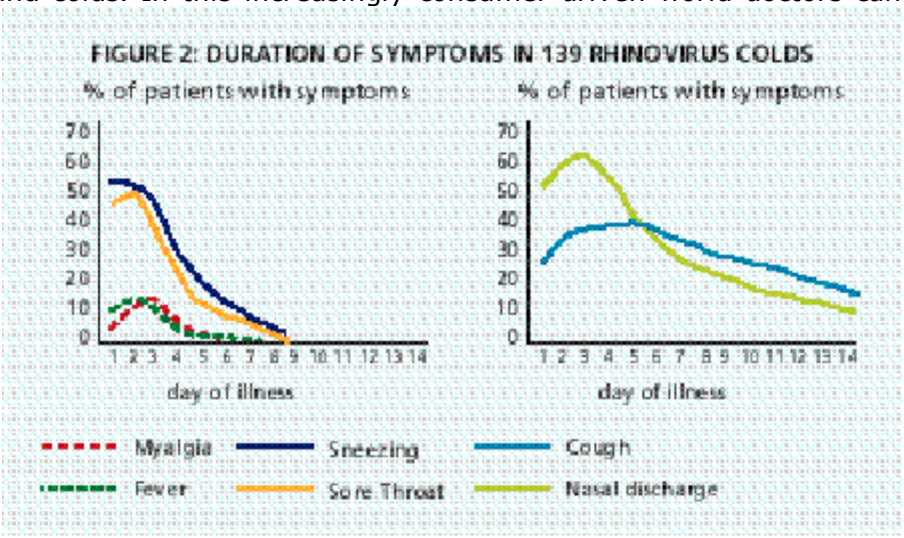
Bacteria or virus?

In clinical practice we are often faced with uncertainty. There are no readily available tests (with the exception of rapid Strep A tests) to help us determine if the patient is suffering from a bacterial or viral infection. Many doctors react to this uncertainty by prescribing antibiotics.

But if we think in terms of syndromes, the infecting agent becomes less important. It is well known that antibiotics are ineffective for uncomplicated acute bronchitis in otherwise healthy individuals, provided there are no abnormal signs in the chest.[13] Other common syndromes, where antibiotics have little or no effect regardless of the infecting agent, are acute sinusitis unless there is fever and facial pain,[14] head colds, coughs and mucopurulent nasal discharges in otherwise well looking children.[15]

Time for change

Many patients have unrealistic expectations about the ability of antibiotics to cure common coughs and colds. In this increasingly consumer-driven world doctors can feel obliged to prescribe antibiotics so as not to appear uncaring or for fear of losing patients. Unfortunately it is all too easy to medicalise these patients, even though they would have improved without treatment. Yet, because they get better while taking an antibiotic, the next time they contract a viral URTI they are more likely to return for the same treatment.



While this may be good for business from the doctor's point of view, it is bad medicine. Studies have shown GPs prescribe antibiotics even when they think they are unnecessary,[16] so the medical profession has made a rod for its own back. We have to change not only our patients' patterns of behaviour but our own as well.

Peer-led small education groups are one of the most effective strategies for changing doctor behaviour. Several IPAs have taken up this model and some have already run modules on antibiotic resistance. Many clinical practice guidelines are available but have limited ability to bring about behaviour change unless they have been developed or modified locally and are endorsed by local opinion leaders. Public education is also clearly needed and this should be on a national basis.

Strategies to reduce prescribing

Objective evidence consistently suggests that doctors overestimate patients' expectations.[16,17] It is worth spending time trying to explicitly identify patients' expectations at the beginning of the consultation. Some may only want a medical certificate. Many patients will want explanation and reassurance.

Patients with respiratory infections are more satisfied if they feel the doctor spends enough time with them and explains their illness, than if they are simply prescribed antibiotics.[18] Doctors should be familiar with the natural history of URTIs (Figure 2) and appreciate that yellow or green sputum and nasal discharge is commonly caused by viral infections and is not necessarily an indication for antibiotics.

Viral URTIs can cause unpleasant and sometimes severe symptoms. Patients are more likely to feel they are being taken seriously if their symptoms are acknowledged. Much can be done to relieve symptoms with advice about appropriate analgesia, decongestants, cough suppressants, throat lozenges, fluids and bed rest.

Explaining to the patient what you are doing and why, while you carry out an examination, helps to demystify the process. A physical examination is powerfully reassuring and will help to allay anxieties if antibiotics are not being prescribed. If you don't think the patient will benefit from antibiotics then convey this in a positive way, perhaps pointing out that, if antibiotics are kept for when they are really needed, they are more likely to be effective.

Clear instructions should be given to the patient about if or when to return for review, particularly if they have persistent fever. For patients who insist on antibiotics even after careful examination and reassurance, a "delayed" prescription can be given as a compromise. Careful patient selection is required though as it devolves responsibility to the patient to decide when or if to start antibiotics.

Conclusion

Antibiotics prescribed for viral infections are not only ineffective but also potentially harmful. They expose the patient to the possibility of oral contraceptive failure, allergic reactions and side effects and increase the likelihood of resistant commensals that may go on to cause invasive infections. Resistant commensals may also be passed onto family members and contacts and fuel the trend towards increasing levels of antibiotic resistance.

GPs prescribe more antibiotics than specialists and hospital doctors put together. We therefore have the potential to make the greatest positive impact on antibiotic resistance by being responsible with our prescribing.

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