11: Antibiotic resistance

Peter J Collignon

Some simple changes to practice could reduce development and spread of antibiotic resistance

BEFORE ANTIBIOTICS were available, bacterial infections such as meningitis and endocarditis were almost uniformly fatal, and common infections such as *Staphylococcus aureus* bacteraemia had a mortality of 80%.[1] One of the major medical advances of the last century was the development of effective antibiotics. However, with widespread use of antibiotics came antibiotic resistance.

Emergence of antibiotic resistance

By the late 1950s, many people with serious *S. aureus* infections had entered a "post-antibiotic" era, as most isolates were resistant to penicillin, the "last-line" antibiotic of the time. Fortunately, in the 1960s, new classes of drugs were developed, such as vancomycin and methicillin, which overcame the problem of resistance. These agents, or their subsequent derivatives (eg, dicloxacillin and flucloxacillin), remain the agents of choice for most *S. aureus* infections today.

Unfortunately, antibiotic resistance has moved on. Increasing numbers of *S. aureus* infections are caused by methicillin-resistant strains (MRSA), including many infections acquired in the community.[2,3] None of the β-lactam antibiotics (including methicillin derivatives and cephalosporins) are effective in these infections. Until recently, this left vancomycin as the last-line antibiotic for hospital treatment of serious MRSA infections. However, although vancomycin was once reliable against all gram-positive organisms, including MRSA and enterococci, increasing numbers of *S. aureus* strains now also respond poorly to this antibiotic.[4] These vancomycin-intermediate *S. aureus* strains (VISAs) have been found in many countries, including Australia.[5] Vancomycin-resistant enterococci (VRE) have also been found in Australia, Europe and the United States.[6,7] Patients with serious infections caused by VRE, such as bacteraemia, have high mortality.[6]

Because of concern about vancomycin resistance, two new agents — quinupristin–dalfopristin and linezolid — were developed and rapidly approved for clinical use. However, the former is not effective against *Enterococcus faecalis*, while resistance to the latter has been detected in bacteria isolated after therapy, including VRE and MRSA.[8,9]

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Abstract

- Antibiotic resistance is a consequence of antibiotic use — we need to use antibiotics less and to use them prudently.

- Plans to combat antibiotic resistance were recently proposed by the World Health Organization, a United States interagency taskforce and the Australian Joint Expert Technical Advisory Committee on Antibiotic Resistance.

- Prudent antibiotic use includes not using antibiotics when benefit is minimal (eg, in many respiratory tract infections), using narrow-spectrum antibiotics whenever possible and using optimal dosages and regimens.

- The need for antibiotic therapy can be reduced by preventing infections through vaccination, infection control measures and improved sanitation.

- Surveillance of antibiotic resistance is needed to target interventions for minimising antibiotic use.

- More research is needed into new antibiotics and regimens and into improving medical devices and protocols to prevent infection.

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The problem of antibiotic resistance also occurs in gram-negative bacteria. There are few or no antibiotics available now (or likely to be available soon) to treat life-threatening infections caused by some of these bacteria. For example, *Acinetobacter baumanii* has caused outbreaks of infections in intensive-care units in Australia, as well as overseas.[10]

Bacteria resistant to "last-line" antibiotics, such as carbapenems (eg, meropenem), glycopeptides (eg, vancomycin), fluoroquinolones (eg, ciprofloxacin) and third-generation cephalosporins (eg, cefotaxime), are often found in Australian hospitals. Some are also found in the community and even in food.[7,11] Many taskforces and committees have reported on the growing problem of antibiotic resistance, including the Australian Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR).[12] Both a United States interagency taskforce and the World Health Organization recently proposed plans to combat antibiotic resistance.[13,14]

Mechanisms of antibiotic resistance

Selective advantage

Most antibiotics modify or interfere with essential functions or structures of bacteria, and many appear to be analogues

of elements of bacterial metabolism or to mimic natural signals. This may explain why the genes encoding resistance may be widespread even before antibiotic use.[15] For example, wild animals in Australia have little or no exposure to antibiotics, yet a study of *Escherichia coli* isolates from kangaroos and wombats found that 3% were resistant to amoxycillin, 2% to cephazolin, 0.2% to tetracycline, and 0.2% to trimethoprim.[15] Antibiotic resistance was also present, albeit at low levels, in other *Enterobacteriaceae*
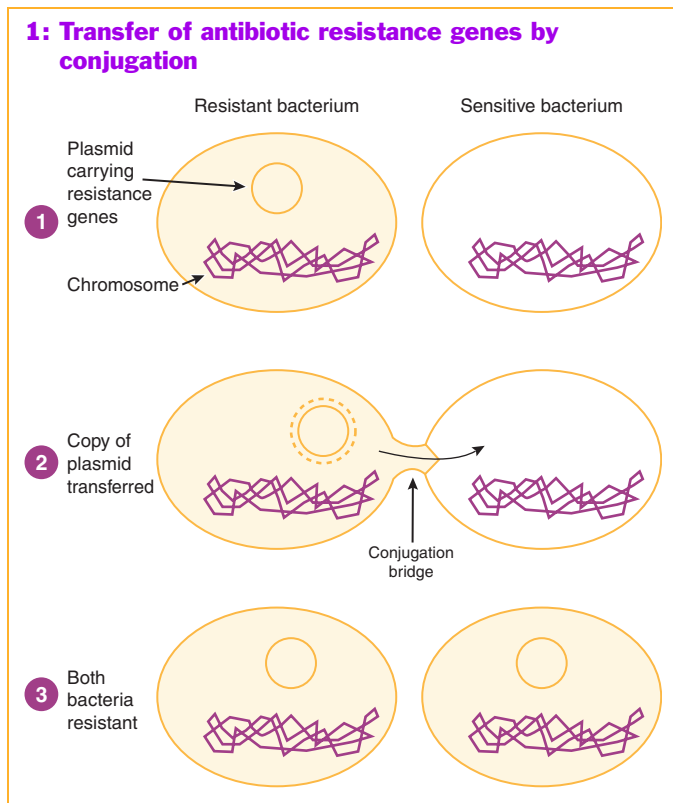
isolates (eg, trimethoprim resistance in 3% of *Enterobacter cloacae* isolates).

However, when antibiotics are used, bacteria with DNA encoding resistance have a selective advantage over sensitive bacteria and can more easily multiply (along with their genetic material). Their larger numbers facilitate their spread from bacterium to bacterium (Box 1), person to person, animal to animal, and within the environment.

For example, MRSA caused infections in hospital patients in India, Turkey and Poland before methicillin had been used in these countries.[16] However, when methicillin and its derivatives became readily available, MRSA strains were encountered much more often.[16] Individual strains spread efficiently not only within hospitals, but also between hospitals and internationally. Indeed, a major hospital epidemic strain of MRSA in the United Kingdom originated in Australia.[17] In addition, strains of MRSA that originated in the community (eg, in Samoa and the Kimberley region of Australia) now cause infections in people who have had no hospital contact in Australia and many other countries.[2,3]

Genetic transfer

Most bacteria have mechanisms that allow them to share genetic material, such as conjugation (Box 1). These mechanisms allow the genes encoding antibiotic resistance to move between bacteria not only of the same species but also of different species and genera. Genetic material encoding resistance is often "clonal" (ie, identical across a wide range of bacteria) and can readily move between bacteria of the same species and different species and genera, especially when carried within a plasmid or transposon. For example, the *vanA* gene, which encodes vancomycin resistance, is carried within a transposon and moves easily between enterococcal species and potentially to other gram-positive cocci, such as staphylococci.[18] Indeed, evidence of transfer of *vanA* from VRE to an MRSA strain was recently seen in a renal dialysis patient in the United States.[19]

1: Transfer of antibiotic resistance genes by conjugation

2: Case history — a consequence of long-term, broad-spectrum antibiotic therapy

Presentation: A 16-year-old boy was referred to a hospital emergency department by his general practitioner after presenting with fever (39°C), rigors and left-sided pleuritic chest pain.

Investigations and history: A chest x-ray showed left lower lobe pneumonia. The boy reported that he was allergic to amoxycillin and cephalosporins (as a child he had developed a rash to these agents). He had been taking daily doxycycline for the previous three months to treat mild acne, which had not responded to self-selected, over-the-counter preparations.

Management and course: He was treated with intravenous erythromycin because of his reported β-lactam allergies, but continued to be unwell, with ongoing fevers and rigors.

The day after admission, both sputum and blood cultures grew *Streptococcus pneumoniae*. After 48 hours, antibiotic sensitivity results showed that the isolate was intermediate-resistant to penicillin, and resistant to both erythromycin and tetracycline. The antibiotic treatment was changed to vancomcyin.

His fever resolved over the next 12 hours, and he made a slow but full recovery over the next week.

■ *This patient developed a life-threatening infection with an antibiotic-resistant strain of* S. pneumoniae. *Because he was likely to be allergic to β-lactams, few options remained for therapy.*

■ *If not allergic to β-lactams, he could have been treated with intravenous penicillin, which remains effective therapy for pneumonia and septicaemia caused by* S. pneumoniae *strains with intermediate penicillin resistance.*

■ *Carriage of the resistant strain probably resulted from the long-term doxycycline therapy. Long-term use of any antibiotic for acne is likely to select resistant strains not only of* Propionibacterium acnes, *but also of other bacteria carried by the patient. Because doxycycline is broad-spectrum, its use helps select strains resistant to other antibiotics, such as erythromycin.*

■ *Mild to moderate acne can usually be successfully treated with combined topical therapy with benzoyl peroxide and retinoic acid, after discussion with a GP on optimal application.[21] Antibiotics should not be prescribed unless absolutely necessary.*

Cross-resistance

To compound the problem of antibiotic resistance, exposure to one antibiotic may help select resistance to others. If an *E. coli* isolate is resistant to a first-generation cephalosporin (eg, cephalexin), then it will also be resistant to all other cephalosporins of the same generation (eg, cephazolin). Furthermore, if an isolate becomes resistant to a third-generation cephalosporin (eg, cefotaxime), then it will also be resistant to all first- and second-generation cephalosporins.

Cross-resistance also occurs across classes of antibiotics. For example, MRSA strains are resistant to methicillin and its derivatives because of changes to the bacterial receptors for these antibiotics (penicillin-binding proteins); these changed receptors have insufficient activity to result in bacterial death when exposed to the antibiotics. As similar receptors are required by all other β-lactams (including cephalosporins and carbapenems), they too are ineffective against MRSA.

The phenomenon of cross-resistance is one of the principal reasons for recommending narrow-spectrum antibiotics to treat infections whenever possible. If resistance develops, then it will usually be to fewer antibiotics than if a broad-spectrum agent had been used.

Bacteria can also be resistant to many different classes of antibiotics ("multiresistant"). An example is *Streptococcus pneumoniae:* some isolates are resistant to ampicillin, erythromycin, tetracycline and trimethoprim–sulfamethoxazole[20] (case history, Box 2). This not only limits the choice of antibiotic therapy, possibly excluding all oral agents, but also means that the use of any of these antibiotics selects for the multiresistant strain ("coselection"), promoting its persistence.

How to avoid antibiotic resistance

The development and spread of antibiotic resistance are consequences of antibiotic use — in medicine, agriculture and other areas, such as aquaculture. To reduce antibiotic resistance, we need to use antibiotics less and to use them prudently. As bacteria do not respect artificial boundaries between environments, this is essential in all areas of use. Strategies to decrease the development and spread of antibiotic resistance are shown in Box 3.

Prudent antibiotic use

In medicine, prudent antibiotic use dictates that we should not use antibiotics unless they improve patient outcome. Not all bacterial infections need antibiotic therapy. For example, in acute bacterial bronchitis and sore throat, any benefit to the patient from antibiotic therapy is small and counterbalanced by the risk of drug side effects, such as rash.[22,23] Interventions other than antibiotics, such as regular analgesia, are more effective in decreasing symptoms.

In addition, when assessing whether antibiotics should be used for common bacterial infections, the population effect must be taken into account, especially in infections that

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3: Strategies for decreasing antibiotic resistance

Prudent use of antibiotics

General
- Use narrow-spectrum agents whenever possible.
- Do not use antibiotics for non-infection-related purposes (eg, to improve gastric motility or as anti-inflammatory agents in humans and for growth promotion in animals).

Therapy
- Treat infections only when this improves patient outcome overall (balance with adverse events; not all bacterial infections need antibiotics).
- Restrict "last-line" antibiotics for serious infections and use only where simpler agents would be ineffective.

Prophylaxis
- Use short courses (single dose is usually sufficient in surgery).
- Give at the correct time (eg, at the time of surgical incision).

Prevention of infection
- Improve infection control and hygiene.
- Improve use of vaccines.
- Improve infrastructure (eg, safe water supply, better hospital design).

Education
- Educate about use of antibiotics, when not to use them, infection prevention strategies.
- Target both healthcare professionals and the general public.

Surveillance
- How much resistance is present, in which bacteria and where?
- How, which, where and in what quantities are antibiotics used?
- Use to devise targeted interventions to minimise antibiotic use.

Research
- New agents and classes of antibiotics.
- New and better vaccines.
- Alternatives to antibiotics for prophylaxis.
- Better use of current antibiotics (eg, shorter therapy).
- Improved medical devices (eg, disinfectant-impregnated intravenous catheters).
- Protocols for improved patient care (eg, urinary catheters in place for shorter periods; remove intravenous catheters when no longer necessary).

4: "Action steps" for doctors to prevent antimicrobial resistance in the community*

- Vaccinate — have influenza vaccine yourself; make sure infants receive Hib (*Haemophilus influenzae* type b) vaccine; give influenza and *Streptococcus pneumoniae* vaccine to at-risk patients.
- Target the pathogen — grow cultures from the patient; target empirical therapy to likely pathogens and definitive therapy to known pathogens.
- Use local data — know your antibiogram (local antibiotic sensitivity profiles).
- It's OK to say "no" to patients with viral infections.
- Use narrow-spectrum antibiotics wherever possible.
- Treat infection, not contamination or colonisation.
- Stop antimicrobial treatment when the infection is unlikely (eg, cultures are negative) or has been treated (often short-course therapy is sufficient).
- Remove the causes of persisting or recurrent infections — remove indwelling catheters; drain abscesses.
- Practise antimicrobial control — engage in local antimicrobial control efforts; use antibiotic guidelines.
- Break the chain of contagion — stay home when you are sick (and recommend that sick patients stay home from work); keep your hands clean; follow good infection control practices; set an example!

*Adapted from the website of the US Centers for Disease Control and Prevention, *"Action steps" for preventing antimicrobial resistance in the hospital.*[13]

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usually resolve spontaneously with little extra benefit from antibiotic use. Antibiotic use exerts selective pressure not only on the pathogen being treated, but also on the patient's normal flora. Antibiotic resistance in *S. pneumoniae* is a rapidly growing problem in the community, both in Australia and abroad[20] (case history, Box 2). An Australian study found that the presence of penicillin-resistant *S. pneumoniae* in the nasal flora of preschool children was significantly associated with their use of β-lactam antibiotics in the preceding two months.[24] The risk that a child carried a resistant strain of *S. pneumoniae* increased by 4% for each day that the antibiotics were used.[24]

When antibiotic therapy is to be used, it should be targeted as far as possible to the pathogen, which may need to be cultured. Narrow-spectrum antibiotics should be chosen whenever possible. Antibiotics should be used in the optimal dosages and regimens, and should be stopped when the infection is treated.

In agriculture, large quantities of antibiotics are used for growth promotion.[7,12] This has contributed to large numbers of antibiotic-resistant bacteria being ingested by humans via the food chain (eg, VRE in Europe[7]).

Preventing infections

Use of antibiotics can also be reduced by preventing infections in the first place. For example, since the introduction of an effective vaccine for *Haemophilus influenzae* type B (Hib) in Australia, so few Hib infections have occurred[25] that antibiotic resistance of this organism is no longer a major issue.

Antibiotic-resistant *Salmonella* species (eg, *Salmonella typhi*) are major causes of illness throughout the world. The problem of *Salmonella* infection is worst where the water supply is contaminated with faecal material from humans or animals. Providing a safe water supply will decrease antibiotic use and the consequent selective pressure on *Salmonella* species and other bacteria carried by patients.

In hospitals, improving infection control practices could prevent many infections and decrease the need for antibiotic therapy (eg, use of aseptic technique for inserting intravenous and urinary catheters, and compliance with handwashing protocols[26]). Specific modifications to medical procedures and protocols could also prevent infections. For example, the incidence of infections associated with intravenous catheters can be reduced by removing the devices when they are no longer essential.[27] Research on the prophylactic use of antibiotics in surgery has shown that rates of postoperative infection are lower if a single dose of antibiotic is given at skin incision than if a longer course is given before and after the procedure — the previously established practice.[28] Following the new guidelines can hugely decrease the amount of antibiotics used for surgical prophylaxis while improving outcomes. More research is needed into improving medical procedures and protocols to reduce infections.

Good hygiene in the home, especially during food preparation and storage, also has the potential to prevent infections, such as *Salmonella* and *Campylobacter* infections, and thereby minimise antibiotic use.

Evidence-based recommendations

- *Antibiotics for sore throat:* These confer some modest benefits. Symptom duration is shortened by 16 hours. In Western societies, protection against complications is achieved only by treating many with antibiotics who will derive no benefit (E1).[23]

- *Antibiotics for acute otitis media in children:* These provide a small benefit, but with an absolute reduction in pain in only 5%. Most cases resolve spontaneously. Seventeen children must be treated to prevent one child having some pain after two days. Antibiotics have no effect on hearing problems or other complications (E1).[29]

- *Antibiotics for acute bronchitis:* These have a modest beneficial effect, but magnitude of the benefit is similar to the detriment from potential adverse effects. Patients with other symptoms of the common cold who have been ill for less than a week are not likely to show any benefits (E1).[22]

- *Antibiotics for the common cold:* Patients receiving antibiotics did no better in terms of cure or improvement than those taking placebo and had significantly more side effects (E1).[30]

- *Antibiotics for acute maxillary sinusitis:* In sinusitis confirmed by aspiration or radiography, penicillin improved clinical cures compared with controls. Current evidence is limited but suggests penicillin or amoxycillin therapy for 7–14 days (E1).[31]

Conclusion

Resistance is a problem not only in bacteria. Whenever agents are used that interfere with the multiplication of organisms, resistance almost inevitably develops. Examples are viruses (eg, HIV), fungi (eg, *Candida* spp.) and herbicide resistance in plants. By using the optimal dosages and regimens, and most importantly by limiting their overuse, the lifetime of these important agents can be extended, and resistance minimised. Specific "action steps" that doctors can take to prevent antimicrobial resistance in the community are shown in Box 4.

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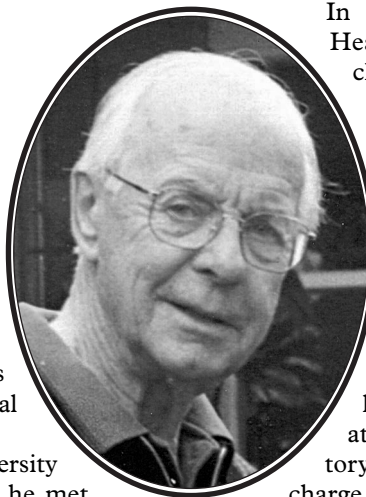
OBITUARY

Eric James Fane De Salis

MB BS DPH FRCPA

BORN ON 18 MARCH 1918 at Gundagai, in New South Wales, Eric De Salis came from a family that had a long association with the pastoral industry in the Monaro district of south-eastern NSW. His early schooling was at a family property, "Soglio", near Michelago. From 1930, he attended Canberra Grammar School, where he excelled in sport (tennis, athletics, cricket and football) and was both a prefect and dux of the school in his final year, 1936.

Eric graduated in medicine from the University of Sydney in 1942. During his student years he met Dorothy Pratt, whom he married in 1943. From 1944 to 1946, he served Australia in the AIF as a medical officer with the field ambulance service in Papua New Guinea and Borneo. As one of the first Australian doctors to use penicillin in the field in Papua New Guinea, he described its effect as "miraculous" in helping desperately ill soldiers to recover in a remarkably short time.

After the war, Eric worked in diagnostic laboratories at the School of Public Health at Sydney University, the Royal North Shore Hospital in Sydney, and the Commonwealth Health Laboratory in Townsville, where he became adept at the laboratory diagnosis of tropical diseases. He gained a Diploma in Public Health in 1946.

In 1950, Eric was appointed Director of the Health Laboratory in Canberra. He expanded its clinical diagnostic services in haematology (his subspecialty), biochemistry and microbiology, and, in 1952, introduced a Pap-smear screening service (one of the first in Australia). He gained his Fellowship of the Royal College of Pathologists of Australasia in 1956.

In 1965, the diagnostic laboratory was relocated to Canberra Hospital, where, in 1968, Eric was closely involved with Dr Bill Coupland in performing one of the first bone marrow transplants in Australia. Two years later, after recovering from a severe heart attack, Eric resigned as director of the laboratory, but continued to work as senior specialist in charge of haematology until his retirement in 1979.

Eric developed motor neurone disease that progressed inexorably. This was a particularly cruel blow for a pathologist and for someone who had excelled in sport. He bore the pain and the restrictions imposed by the disease without complaint, showing a quiet fortitude and remarkable courage up to the time of his death on 14 February 2002.

Eric's selflessness and modesty as a professional colleague were widely acknowledged, as were his skills in many fields of pathology and his prompt response to calls for assistance, at any hour, at Canberra Hospital. He was respected by all who knew him.

Anthony J Proust