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Antibiotic resistance: how it arises, the current position and strategies for the future

A detailed review of the current position regarding antibiotic resistance and how it arises, and an outline of future strategies to tackle this global problem

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After 70 years of antibiotic therapy, the threat of untreatable infections is again a reality with resistance to antibiotics increasing in both Gram positive and Gram negative bacteria.

Antibiotic-resistant bacteria cause both community and healthcare associated infections, presenting challenges in treatment and management. The development of new and novel antibiotics, particularly for Gram negative bacteria, is worryingly lacking.

This article reviews the current situation and examines future strategies to tackle the continued threat of bacterial resistance.

INTRODUCTION

Despite the availability of antibiotics, infections acquired in the community or related to healthcare can still cause significant morbidity and even mortality.

The emphasis on healthcare associated infections (HCAI) has led to a focus on Gram positive bacterial infections such as MRSA and *Clostridium difficile*. Gram negative infections, including *Pseudomonas aeruginosa* and *Escherichia coli*, have received less attention, despite being important causes of both HCAIs and community acquired infections.

Antibiotic-resistant strains of both Gram positive and Gram negative cause challenges in treatment as well as having the potential to cause community and healthcare outbreaks. Resistance to antibiotic treatment is an ever increasing risk that requires novel thinking in antibiotic and other therapies, as well as in preventative measures.

This article reviews the development of antibiotics and antibiotic resistance, and the significance and treatment of Gram positive and Gram negative infections, including resistant strains. It also examines what can be done to address the continued threat of antibiotic resistance.

ANTIBIOTICS AND BACTERIAL RESISTANCE

Before antibiotics were introduced, medical treatments for bacterial infections were limited. Lancing, surgical drainage and direct application of antiseptics could be used for superficial or localised infections. Systemic infections such as bacteraemia were likely to be fatal.

The discovery of antibiotics is generally accredited to Alexander Fleming, who made the accidental discovery of penicillin through the contamination by the mould penicillium of a laboratory plate growing staphylococci. The first reported clinical use of penicillin was in 1941, with the drug entering widespread use in 1944 following work by Florey and Chain. Following this "miracle" discovery, many more antibiotics have been developed from natural substances as well as being synthetically produced.

Antibiotics are either bacteriostatic (prevent bacterial reproduction) or bactericidal (destroy the bacterium). They work in a variety of ways including:

- Preventing cell wall formation – penicillins, cephalosporins and glycopeptides (such as vancomycin and gentamicin);
- Altering cell membrane permeability – cyclic peptides, for example, polymyxins;
- Interfering with protein synthesis – tetracyclines, aminoglycosides, macrolides, fusidic acid and mupirocin;
- Interfering with nucleic acid synthesis – sulphonamides, rifamycins and nitrofurans.

Antibiotic resistance is the ability of a microorganism to withstand the effects of antibiotics.

This can be intrinsic, in that bacteria have innate properties that do not allow the antibiotic to work. For example, vancomycin, which prevents cell wall formation in Gram positive bacteria, is not effective against Gram negative bacteria because their cell wall composition is different.

Resistance can also be acquired. Here, bacteria that could once have been treated with an antibiotic (commonly referred to as "sensitive") become resistant. An example is *Staphylococcus aureus* that has become resistant to meticillin – MRSA. Acquired resistance occurs through spontaneous genetic mutation or the transfer of genetic material from other resistant organisms. The latter occurs in a variety of ways:

- Transformation – the acquisition or uptake of resistant genetic material from the environment around the bacteria;
- Transduction – the transfer of genetic material through infection by a virus (bacteriophage);
- Conjugation – the transfer of genetic material directly from one bacterium to another through direct cell to cell contact. This is not species specific – resistance can be passed between different strains and species of bacteria. This method of transfer is particularly relevant to Gram negative bacteria that have extended-spectrum beta-lactamase (ESBL) producing enzymes.

PRACTICE POINTS

- **Despite the availability of antibiotics, infections acquired in the community or related to healthcare can still cause significant morbidity and even mortality.**
- **Antibiotic-resistant strains of both Gram positive and Gram negative bacteria present challenges in treatment and have the potential to cause community and healthcare outbreaks.**
- **Gram negative infections are a significant cause of healthcare associated infection although other infections receive more attention.**
- **Development of antibiotics for Gram negative infections is lacking.**
- **Strategies to address antibiotic resistance must focus on: infection prevention measures; novel technologies; financial support for antibiotic development; good surveillance systems; more timely diagnosis of infections; and appropriate prescribing of existing antibiotics.**

The mechanisms by which bacteria can withstand the effects of antibiotics generally fall into four categories (Box 1).

The World Health Organization (2001) has recognised resistance as a global problem that needs urgent action. Antimicrobial resistance is a problem in hospitals and the community that requires a coordinated and multifaceted approach to address it.

ANTIBIOTIC RESISTANCE IN GRAM POSITIVE BACTERIA

In 2007, 10 per cent of *Streptococcus pneumoniae* in Europe were resistant to penicillin and 16 per cent were resistant to erythromycin (European Antimicrobial Resistance Surveillance System, 2008).

S. pneumoniae is a common cause of infection in older people, children and patients with compromised immunity. Infections range from sinusitis and otitis media to invasive bloodstream infection and meningitis.

An estimated 25 per cent of community acquired pneumonia is due to pneumococcal infection, accounting for more deaths than any other vaccine-preventable bacterial infection (Todar, 2009). Pneumococcal vaccine is available for children and adults at greatest risk of serious infection.

The first report of meticillin-resistant *Staphylococcus aureus* (MRSA) in 1961 came only two years after the antibiotic was introduced into general use.

The proportion of *S. aureus* invasive infections that are due to MRSA ranges from none in some northern European countries to 50 per cent in southern European ones, with the UK reporting 25–50 per cent as resistant (EARSS, 2008). All UK countries are reporting a falling trend in MRSA bloodstream infections including a 34 per cent reduction in one year (Health Protection Agency, 2009).

S. aureus can cause superficial infections such as boils or styes, as well as more serious infections including pneumonia, urinary tract infection, osteomyelitis, endocarditis and bacteraemia.

Community strains of MRSA have spread widely in the US while in the UK infections from MRSA in the community are still predominantly caused by hospital strains of the bacteria (Rollason et al, 2008). *S. aureus* resistance to glycopeptides (such as vancomycin) remains rare, with only four confirmed cases reported in Europe in 2007 (EARSS, 2008).

Enterococci are normally present in the gut flora of humans and other mammals.

BOX 1. MECHANISMS OF ANTIBIOTIC RESISTANCE

The four categories are:

- **Preventing drug entry by altering cell permeability;**
- **Preventing the drug from reaching the target site by trapping it within the cell or pumping it back out (efflux pumps);**
- **Inactivating or modifying the drug by using enzymes;**
- **Altering the drug target site.**

Although they are not as likely to cause disease as some other bacteria, they can cause a range of infections including wound and urinary tract infections, endocarditis, bacteraemia and meningitis. The majority of enterococcal infections in humans are caused by *Enterococcus faecalis* and *Enterococcus faecium*.

Enterococci are naturally resistant to a wide range of antibiotics, including penicillins and cephalosporins, and a major concern is their high affinity for acquiring resistance by conjugation, transduction and mutation. Transfer of vancomycin resistance from enterococci into *S. aureus* has been demonstrated and the emergence of MRSA with reduced susceptibility to vancomycin has been reported (Hiramatsu et al, 1997). Vancomycin resistance rates are reported to be 13–67 per cent in *E. faecalis* and 0–37 per cent in *E. faecium* (EARSS, 2008).

ANTIBIOTIC RESISTANCE IN GRAM NEGATIVE BACTERIA

Although Gram positive bacteria have attracted much attention in terms of recent infection prevention activities, Gram negative infections are also an important cause of healthcare associated and community acquired infections.

Escherichia coli

Escherichia coli and related Gram negative bacteria are commonly found in the human gut. *E. coli* is a common cause of community acquired and hospital-associated urinary tract infections. They are also a common cause of neonatal meningitis and cause surgical wound infections and abscesses in a variety of organs and bacteraemia; *E. coli* is now the most frequent cause of bacteraemia in the UK (HPA, 2007).

Resistance to cephalosporins (including cefotaxime and ceftazidime) was reported in up to 12 per cent of *E. coli* bacteraemias in 2006, an increase from 3 per cent in 2002 (HPA, 2008). Highly resistant strains of *E. coli* have been widespread in the UK since 2003. These are known as extended-spectrum beta-lactamase (ESBL) producers and are able to break down a wider range of antibiotics including penicillins as well as cephalosporins.

Additional resistance to fluoroquinolones, aminoglycosides, tetracycline and trimethoprim has also been reported, with 2.5 per cent of *E. coli* in Europe resistant to four types of antibiotics (EARSS, 2008).

Infections with ESBL-producing *E. coli* have become widespread in the UK, with outbreaks of community and hospital urinary tract infections reported.

Klebsiella pneumoniae

Like *E. coli*, klebsiella are commonly found in the human gut, and can also be found in the upper respiratory tract and on the skin of hospital patients.

Klebsiella pneumoniae infections occur in both community and hospital patients, commonly causing urinary tract and respiratory tract infections; community acquired respiratory tract infections have a mortality rate of up to 50 per cent. These bacteria can be an important cause of hospital associated infections, particularly in patients with poorer immune function, causing wound infections, urinary tract infections, pneumonia and bacteraemias.

Klebsiella pneumoniae are naturally resistant to aminopenicillins (ampicillin) but can also be resistant to multiple antibiotics and have ESBL-producing strains, with transfer of resistance genes via conjugation taking place more readily than with *E. coli*.

Over 30 per cent of klebsiella in Europe do not show acquired resistance. However, 14 per cent have resistance to three groups of antibiotics that include fluoroquinolones, cephalosporins and aminoglycosides (EARSS, 2008). Carbapenems (such as meropenem) are the antibiotics often used for life threatening infection in patients with highly resistant klebsiella infections.

Although resistance to carbapenems is uncommon, several European countries have reported resistance, with rates varying from 1–42 per cent (EARSS, 2008).

Pseudomonas aeruginosa

Pseudomonas aeruginosa is naturally present everywhere, particularly in wet environments. In humans, it can infect almost any external site or internal organ.

Hospital associated infections are more common than those acquired in the

community, and range from urinary tract infections, chronic wound (such as pressure ulcer) infections to eye and burn infections. *P. aeruginosa* does not commonly cause pneumonia or bacteraemia but, when it does, it is often associated with a poor outcome.

It is naturally resistant to a number of antibiotics by preventing the drug molecules from entering the cell. It can also acquire resistance through transformation, transduction and conjugation, so resistance can readily occur during antibiotic treatment.

In the UK, *P. aeruginosa* resistance to gentamicin and imipenem was lower in 2008 than in 2007, while resistance to other antibiotics (including ciprofloxacin, ceftazidime and meropenem) remained stable (HPA, 2008). Across Europe, 17 per cent of *P. aeruginosa* bacteria are multiresistant (EARSS, 2008).

Acinetobacter baumannii

Acinetobacter are ubiquitous in the environment and can be carried on human skin. *A. baumannii* can cause hospital associated infections including meningitis, pneumonia, wound infections and bacteraemias, particularly in critical care and burns patients.

Multiresistant *A. baumannii* are resistant to aminoglycosides and cephalosporins: some are also resistant to imipenem or meropenem. Rates of resistance to ceftazidime in Europe range from 15 to 97 per cent and to imipenem from less than 1 per cent up to 85 per cent (Souli et al, 2008).

With highly resistant strains, antibiotic use is limited. However, polymyxins have good in vitro activity against *A. baumannii,* although information on clinical use is limited as it is no longer routinely used in the UK due to variable clinical outcomes and a slight risk of toxicity (Chopra et al, 2008).

CURRENT AND FUTURE TREATMENT OF GRAM NEGATIVE INFECTIONS

Choice of antibiotic is influenced by the nature of the bacteria causing the infection (for example, whether Gram negative or Gram positive), the site of infection and patient factors (such as allergy, pregnancy or severity of infection).

Where infection is suspected but the causative microorganism has not been identified, antibiotics with a broader spectrum of antimicrobial activity will be prescribed.

Once a causative microorganism has been identified, antibiotic sensitivity tests will be carried out and prescribing can be amended if necessary to ensure that antibiotics are targeted appropriately.

BOX 2. DESIRABLE FEATURES OF ANTIBIOTICS

- Antibiotics should have as many of the following as possible:
- Non toxic and without undesirable side effects;
- Non allergenic;
- Should not alter the normal bacterial composition of the body;
- Should be able to reach the part of the body where the infection is located;
- Inexpensive and easy to use;
- Chemically stable with a long shelf life;
- Microbial resistance is uncommon and unlikely to develop.

Source: Todar (2009)

For an antibiotic to be clinically useful it should have as many of the characteristics outlined in Box 2 as possible.

The agents that have mainly been used for treating Gram negative infections are:

- Aminoglycosides – such as gentamicin and amikacin;
- Third generation cephalosporins – for example, cefotaxime and ceftriaxone;
- Other beta-lactams – such as aztreonam;
- Quinolones – for example, ciprofloxacin and levofloxacin.

However, as noted above, resistance to many of these antibiotics is now evident and alternative antibiotics must be used. For ESBL-producing Gram negative bacteria, it is recommended that: urinary tract infections are treated with quinolones; bacteraemias, hospital acquired pneumonia and intra abdominal infections with carbapenems; and meningitis with meropenem (Paterson and Bonomo, 2005).

The carbapenem group of antibiotics includes imipenem, ertapenem, doripenem and meropenem. Administration is intravenous and their mode of action is to interfere with production of the bacterial cell wall, being bactericidal.

Resistance to carbapenems already exists in some Gram negative bacteria including *P. aeruginosa,* acinetobacter species and *K. pneumoniae* (Centers for Disease Prevention and Control, 2009). Although resistance remains rare, there is concern that carbapenem resistance is increasing in *A. baumannii* (HPA, 2004). As the route of administration is IV, carbapenems will generally be used in hospitals for patients with significant infection. In many hospitals, their use is restricted to reduce the risk of further resistance developing.

Anti-pseudomonal penicillins that can be used for *P. aeruginosa* as well as some other Gram negative infections include ticarcillin and piperacillin. Piperacillin is combined with tazobactam, and ticarcillin with clavulanic acid. Like carbapenems, they are administered by the IV route and will, therefore, generally be used in hospital settings. For pseudomonal septicaemia, they should be given with an aminoglycoside (such as gentamicin) to achieve a synergistic effect, as the action of the two drugs together gives a greater effect than either of them alone (British National Formulary, 2009).

Tigecycline entered clinical use in 2005. It is the first antibiotic to be launched in the glycylcycline group, which are similar in structure to tetracyclines.

Tigecycline is bacteriostatic, and inhibits production of protein in the bacterial cell. It is administered by the IV route. Although effective against a wide range of resistant Gram negative bacteria, it is of limited use for infections of the urinary tract, where most of the ESBL-producing Gram negative bacterial infections are located (Livermore, 2005). It is not effective against *P. aeruginosa* (Bhattacharya et al, 2009). Resistance to *A. baumannii* and *K. pneumoniae* in the laboratory setting and in clinical trials have been reported (Navon-Venezia et al, 2007; Livermore, 2005).

Polymyxin B and colistin are from the polypeptide group of antibiotics developed in the late 1940s but have not been clinically used widely in recent years because of concerns over toxicity (Arnold et al, 2007).

They are rapidly bactericidal and act by altering the permeability of the outer membrane of bacterial cells. They have good activity against most clinically relevant Gram negative bacteria. Resistance to Gram negative bacteria, including *P. aeruginosa*, *E. coli* and *K. pneumoniae*, is reported but remains uncommon due to their infrequent use in recent years (Zavascki et al, 2007). Colistin is available as an IV preparation and as a powder for nebuliser solution and polymyxin B is available in powder form for intramuscular or IV injection.

New developments

While a number of antibiotics for Gram positive infections are in the later stages of development, the only one imminently

expected for worldwide use for Gram negative bacteria is faropenem. Development of an oral carbapenem is in progress.

These products, together with the other recently launched antibiotics for Gram negative infections, are related to or derivatives of existing groups of antibiotics in which Gram negative bacterial resistance is also present.

The development of new antibiotics is costly and time-consuming, giving limited financial return for the outlay. In addition, prudent antibiotic prescribing to reduce risk of other infections (such as *C. difficile*) and the need for antibiotics with a narrow spectrum of activity means their development is not financially viable for the pharmaceutical industry (Finch and Hunter, 2006). This lack of development of antibiotics for Gram negative bacterial infections is a cause of major concern internationally (Chopra et al, 2008).

Other novel technologies, which aim to prevent rather than cure infections, may be useful in reducing antibiotic use and delay the inevitable development of resistance.

Vaccines have proven invaluable in controlling and eliminating serious infections, including smallpox. They have also been shown to have an impact outside the age group being vaccinated. For example, the pneumococcal vaccine given to children also reduced infection rates in older age groups and an associated reduction in macrolide resistance was seen (Stephens et al, 2005).

Clinical trials of vaccination against *P. aeruginosa* have taken place. Vaccines against other Gram positive and Gram negative bacteria are in the early stages of development (Finch and Hunter, 2006).

Since many infections caused by Gram negative bacteria are opportunistic – affecting people with poor immunity resulting from underlying conditions – cases of Gram negative bacterial infection are likely to increase as advances in medical treatments lead to increased survival of patients with severe underlying disease. Given this, and the increasing resistance to commonly used treatments, all options to preserve the effectiveness of existing antibiotics need to be deployed.

FUTURE STRATEGIES

As new antibiotics enter clinical use, it will be a matter of time before resistance to these drugs occurs due to the nature of evolution. For future strategies, see Box 3.

Developing new antibiotics will require public funding and greater involvement of non-profit-making organisations (such as universities), with a focus on the Gram negative bacteria (Chopra et al, 2008). Collaborations between microbiologists and biochemists will be essential in supporting the discovery of new classes of antibiotics.

Increased infection prevention and control measures in healthcare settings will be necessary not only to reduce the spread of existing resistant bacteria but also to reduce all HCAIs and, therefore, reduce antibiotic prescribing. Other preventative measures, such as vaccination, should also be pursued.

Tighter control over antibiotic prescribing is also essential. This can be supported by rapid and sensitive diagnostic testing, enabling more timely identification of the bacteria causing infection. This also further supports the use of antibiotics with a small spectrum of activity.

Surveillance systems will be essential for tracking resistance patterns.

BOX 3. STRATEGIES FOR THE FUTURE

Strategies to ensure infections remain treatable in the future will need to include:

- **Infection prevention measures;**
- **Strict control of antibiotic prescribing;**
- **Development of new and different antibiotics;**
- **Consideration of new technologies.**

CONCLUSION

In fewer than 70 years, we have gone from the widespread launch of the "wonder drug" penicillin to considering what the future may be for antibiotics. The challenges are immense. Nurses can play a key role in helping to reduce antibiotic resistance by strict adherence to infection control measures and ensuring antibiotic prescriptions are reviewed regularly by medical staff. However, it will require global initiatives to ensure we do not return to the conditions of the pre-1940s era. ●

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