Antimicrobial resistance – challenges for the 21st century

KEY WORDS
- Antibiotics
- Antimicrobial resistance
- Misuse/overuse of antibiotics

Antimicrobial drugs are medicines that are active against a range of infections, such as those caused by bacteria (antibiotics), viruses (antivirals), fungi (antifungals) and parasites (including antimalarials). Increasing resistance to these drugs has been widely reported and the magnitude of problems this will cause has now been accepted. In her article, Val Edwards-Jones gives an overview of what antimicrobial resistance is, why it has arisen, why it is a problem and what can be done to counteract it. The article makes essential reading for clinicians involved in wound care to understand the issues involved, the challenges ahead and what the potential solutions might be.

VAL EDWARDS-JONES
Emeritus Professor of Medical Microbiology, Manchester Metropolitan University; Visiting Professor, Skin Integrity and Infection Prevention Institute, University of Huddersfield

Antimicrobial resistance (AMR) is increasing among common pathogens associated with healthcare-associated infections. Although AMR is seen in all groups of microorganisms (bacteria, fungi and viruses), antibiotic resistance is causing the most concern. This is because bacterial infections have been successfully treated and numerous lives saved over the last seventy years. If we have no antibiotics to treat patients effectively this will have a huge impact on modern medicine as we know it and the possibility of returning to a pre-antibiotic era.

Antimicrobial agents can be broadly grouped into different categories and are described in *Table 1*.

In the UK, there has been a reduction in the number of antibiotics available for prescription compared to twenty years ago because common bacterial pathogens have developed resistance to first generation antibiotics. In addition, many large pharmaceutical companies have stopped developing new antibiotics because the cost of development of a single antibiotic can be cost prohibitive (Bax and Green, 2015). The UK Government has responded by establishing an AMR Strategy 2013–2018. The UK AMR Strategy has three major aims, namely:

- To improve the knowledge and understanding of AMR
- To conserve and steward the effectiveness of existing treatments
- To stimulate the development of new antibiotics, diagnostics and novel therapies (Department of Health, 2013).

BRIEF HISTORY OF ANTIMICROBIAL AGENTS

Tetracyclines have been traced back to 350–550 AD in human skeletal remains from ancient Sudanese Nubia (Bassett et al, 1980). In addition, tetracycline has been demonstrated in bones from skeletons found in Egypt using fluorochrome labelling (Cook et al, 1989; Aminov, 2010). This implies that humans were exposed to these antimicrobials in some form in the diets of these populations. Whether this was intentional or accidental is not known but demonstrates their presence in history.

Knowledge of antimicrobial agents was not really further described until the discovery of microorganisms and infectious diseases in the mid-sixteenth century when Anton Van Leeuwenhoek described bacteria, fungi and protozoa from a variety of sources with his crude first microscope (Wainright and Lederburg, 1992). The next two hundred years saw a plethora of diseases being described by Pasteur, Koch, Jenner and Lister. Vaccines and infection control were introduced to counteract the diseases. Semmelweiss introduced hand washing (circa 1861) which successfully reduced cross infection

Table 1. Groups of antimicrobial agents	
Antimicrobial agents Antibacterial agents, e.g. antibiotics Antiviral agents Antifungal agents Antiparasitic agents	Systematically and topically administered
Biocides Antiseptics and disinfectants	Usually topically administered
Biologics E.g, natural defensins (peptides), reactive oxygen species (ROS)	Usually topically administered

and this became a widely accepted practice. In 1867, Joseph Lister went further and reduced mortality by covering wounds with antiseptic dressings mainly containing carbolic acid or phenolics (Lister, 1867).

Early development of antibiotics is usually credited to Fleming in 1929, however, other antimicrobial agents were available prior to its commercialisation in 1939. In 1891, Paul Erlich (a German chemist) used dyes (methylene blue) to treat malaria and, in 1910, arsenic compounds (Salvarsan) to treat protozoa and syphilis. In 1935, Domagk used the red dye Prontosil, (a sulphonamide compound) to successfully treat respiratory infections (Wainwright and Lederburg, 1992). Following the successful commercialisation of Penicillin in 1939, a number of other classes of antibiotics were developed for the treatment of infectious disease.

Interestingly, Fleming predicted the emergence of penicillin-resistant strains in an interview following receipt of his Nobel prize on 11th December 1945 (Fleming, 1945). He stated that 'There is the danger that ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant'. Unfortunately, this was to become a reality and shortly after the introduction of antibiotics, AMR was observed.

Antimicrobial agents are a generic term for different groups of chemical compounds that can kill or inhibit the growth of microorganisms. Antimicrobials include antibiotics, anti-viral agents, anti-fungal agents, antiparasitic agents, disinfectants, antiseptics and naturally occurring compounds (biologics) such as reactive oxygen species (ROS), defensins and antimicrobial peptides (AMPs) *(Table 1)*.

AMR has been found in all groups of antimicrobial agents but is most notable in antibiotics. Antibiotics are natural substances obtained from certain fungi and bacteria that can inhibit the growth of bacteria. They have a specific target site and mode of action where they exert their effect within the bacterial cell. These are listed in *Table 2*. Many of these antibiotics have low toxicity because the target site is present in the prokaryotic bacterial cell but not present in the eukaryotic human cell hence their widespread use for treatment of a plethora of bacterial infections and infectious disease. The best example of this is penicillin where the target site is peptidoglycan in the bacterial cell wall. This polymeric substance is only found in bacterial cells NOT in human cells, therefore, penicillin is relatively non-toxic (unless the patient is allergic to the compound).

Between 1940 and 1962, over 20 new classes of antibiotics were introduced, however since then, only two new classes have reached the market. Modifications to existing classes kept pace with the emergence of AMR until 10–20 years ago and now, unfortunately, these are not being developed fast enough to stem the tide of antibiotic resistance, particularly among Gram-negative bacteria (Coates et al, 2011). A huge effort by all Governments in the form of finance, legislation and providing the industry with real incentives may reverse this. The pharmaceutical industry needs to re-enter the market on a much larger scale to develop new antibiotics. Clinicians need to use antibiotics more appropriately and follow prescribing policies and they should be withdrawn from animal husbandry and agriculture. In addition, improved rapid diagnoses of infection need to be developed and implemented wherever possible to prevent inappropriate use of antibiotics. The alternative if we do not act now is medicine without effective antibiotics.

WHAT IS AMR?

AMR is a natural process whereby microorganisms evolve to resist an antimicrobial agent making them ineffective. It is defence mechanism used by one microorganism to enable survival in a hostile environment where other microorganisms are competing for nutrients and position in the environment the organism exists in. For example, in the soil, some bacteria and fungi are naturally resistant to a number of antimicrobial agents, because other groups of bacteria may produce

Table 2. Classes of antibiotics and their bacterial target site	
Classes of antibiotics	**Bacterial target site**
Penicillins, Cephalosporins, bacitracin, vancomycin	Cell wall synthesis
Polymixin, Colistin	Cell membrane function
Aminoglycosides (e.g. gentamicin), macrolides (e.g. erythromycin), lincosamides (e.g.clindamycin) streptogramins (e.g. quinupristin/dalfopristin), chloramphenicol, tetracyclines	Protein synthesis
Sulphonamides, trimethoprim	Metabolic pathways
Quinolones, metronidazole, rifampicin	Nucleic acid synthesis

Box 1. The key areas needed to tackle AMR globally (O'Neill et al, 2016)

- A global public awareness campaign
- Improve sanitation and prevent the spread of infection
- Reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment
- Improve global surveillance of drug resistance and antimicrobial consumption in humans and animals
- Promote new, rapid diagnostics to reduce unnecessary use of antimicrobials
- Promote development and use of vaccines and alternatives
- Improve the number, pay and recognition of people working in infectious disease
- A global innovation fund for early stage and non-commercial R&D
- Better incentives to promote investment for new drugs and improving existing ones

antibiotics to kill off these competing bacteria. If they are resistant to the antibiotics produced then they can survive in the soil alongside those strains that are producing the antibiotic. AMR in the healthcare environment arises from selective pressure on microbial populations by overuse of antibiotics allowing resistant strains to survive and proliferate. Resistance to antibiotics may be a natural property of the bacterium itself (physical properties e.g. cell wall/cell membrane properties) or the bacterium may acquire resistance through mutation or horizontal transfer of the AMR genes from one bacterium to another (Tenover et al, 2006).

Bacterial resistance mechanisms

There are four documented resistance mechanisms in bacteria:

- The inactivation or modification of the antibiotic (usually by secreted enzymes, e.g. beta-lactamases)
- An alteration of the target site of the antibiotic that modifies its binding capacity (usually by mutation e.g. gentamicin)
- The synthesis of resistant metabolic pathways (e.g. folic acid synthesis, e.g. sulphonamides)
- Reduced intracellular antibiotic accumulation by lack of entry through decreasing cell permeability and/or increasing active efflux (pumping out the antibiotic from the cell, e.g. tetracyclines).

Other resistance mechanisms may be used by viruses or fungi. Any bacterial species can acquire a single resistance gene or multiple resistance genes if conditions are optimal, allowing the acquisition of multiple resistance traits over time.

Unfortunately, since the introduction of the various antibiotics, resistance has been detected in all major groups of bacteria. Some bacterial infections, such as Gram-negatives, are already very difficult to treat, for example, *Pseudomonas aeruginosa* and metallo-β-lactamase producing pathogens which neutralise carbapenems (Kumarasamy et al, 2010), while others, such as Gram-positive staphylococcal infections like methicillin-resistant *Staphylococcus aureus* (MRSA) still show some susceptibility to a range of old and new antibiotics. Multi-drug antifungal resistance has been seen in yeasts *(Candida auris)* (Chowdary et al, 2017) and anti-viral resistance identified in Herpesviruses and hepatitis B (Strasfeld and Chou, 2010) as well as influenza and other viruses.

WHY IS AMR A PROBLEM?

Although AMR is a naturally occurring process, today it is a threat for two main reasons. The first is that the use of antibiotics in healthcare and uncontrolled use in agriculture and animal husbandry has increased so much in the last few decades, that the exposure to bacteria has led to AMR selection at an alarming rate. Secondly, there are limited numbers of new antibiotics under development and this is worrying for the future. AMR is growing at an alarming rate.

In 2014, the UK Government commissioned a review on AMR by Lord O'Neill to be completed in 2016 (O'Neill et al, 2016). The report advises on how to tackle the problem globally and recommends a number of key areas that require immediate action in order to minimise the impact of AMR on human and animal health (*Box 1).*

AMR infections are thought to be responsible for over 5,000 deaths in the UK, 50,000 deaths across Europe and the USA and an estimated 700,000 deaths globally each year (O'Neill et al, 2016). Early research commissioned by the O'Neill review suggests that if the world fails to act to control resistance, this toll will exceed 10 million each year by 2050 *(Figure 1)* and have cost the world over 100 trillion USD in lost output (O'Neill et al, 2016).

AMR varies across different countries and regions of the world and is linked to the extent of use of

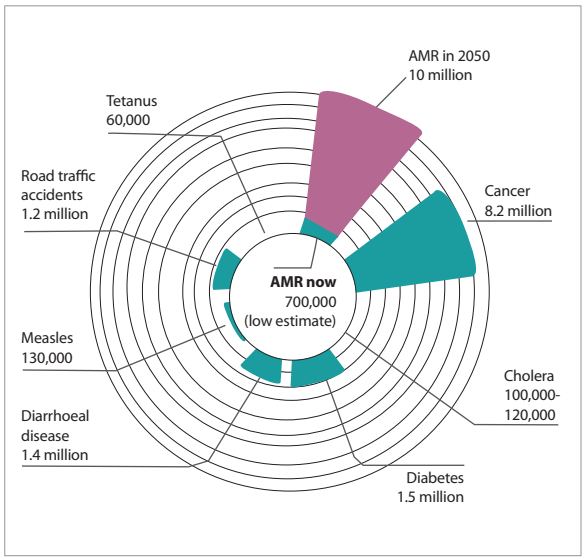

Figure 1. Estimated death toll per year and category now, with AMR-related deaths estimated to exceed 10 million a year by 2050 (O'Neill, 2016)

antibiotics in these countries or regions. However, international travel means that AMR has spread to other countries that are now putting controls in place to use their antibiotics in an appropriate manner. Not all countries monitor their antibiotic usage and surveillance of AMR is not always carried out.

Strategies for reduction in AMR are being mirrored across the developed world inside and outside Europe. All AMR strategies for each country are published and freely available online at the European Centre for Disease Prevention and Control (2016) website.

In the UK, there has been a fall in the number of prescriptions issued for antibiotics following the implementation of antibiotic stewardship across the healthcare environments in primary, secondary and tertiary care facilities (O'Neill, 2015b). Doctors prescribed 2.2 million fewer antibiotics between 2014 to 2015 than in previous years (National Institute for Health and Care Excellence [NICE], 2016)

OVERUSE OF ANTIBIOTICS IN ANIMALS

Data suggests that much of the overuse of antibiotics globally is in animals rather than humans and that much of this is used for promoting the growth of animals rather than treating sick animals (O'Neill, 2016). The development and spread of drug resistance in this area have been overlooked for a long time but is now being addressed globally. Latest industry figures show the UK pig industry reduced its antibiotic usage by 28 per cent in 2017, in addition to the 34 per cent cuts it made in 2015 and 2016 (Park, 2018).

OVERUSE OF ANTIBIOTICS IN MAN

The overuse of antibiotics in man has occurred because many infections are treated empirically with a broad spectrum antibiotic, whilst the clinician is waiting for the results from the laboratory. In addition, many clinicians do not always change the antibiotic therapy once the results are received as the infection may have resolved or clinically improved. It is therefore postulated that improved diagnosis will help reduce this overuse (O'Neill, 2015a). A point of care diagnostic tool that helps the clinician to determine whether the patient has a bacterial or viral infection would be advantageous as this could negate the use of empirical antibiotic treatment when the patient has a viral infection and save many unnecessary antibiotic prescriptions being issued. Detection of infection at the earliest opportunity could prevent the wound from deteriorating further and allow appropriate intervention to be initiated.

In wound care, diagnosis of wound infection can be difficult and resultant microbiological sampling does not always help the clinician. Wound infection is diagnosed clinically based on the criteria outlined by Cutting and Harding in 1994 and refined by Cutting and White in 2004. If the patient has an infected acute wound (less than 30 days duration) then swabbing the wound is essential and the infection is usually caused by a single pathogen (James et al, 2008). Treatment with recommended systemic antibiotics often resolves the infection. In the case of chronic wounds (greater than 30 days duration) then wound swabbing can be unhelpful as over 80% of chronic wounds contain biofilm, with no predominant pathogen causing the infection (Malone et al, 2017). Antibiotic treatment often fails to resolve the chronic wound and the involvement of biofilm as a vehicle of antibiotic resistance and a mechanism for bacterial tolerance is underappreciated (Bowler, 2018). Non-antibiotic antimicrobial interventions are likely to become the means of resolving these non-healing chronic wounds and biofilm-based wound care currently, is certainly the way forward (Wounds UK, 2017).

AMR wound pathogens such as MRSA, and MDR Gram-negative organisms (Bowler et al, 2012) need to be removed from the wound environment wherever possible as any of these pathogens could enter the bloodstream from the infected wound. This would leave only limited choices for systemic treatment and, if the patient develops sepsis, then the risk of fatality is high.

As there are over 2.2 million people undergoing some form of wound management in the UK at a cost of approximately £5.3 billion pounds (Guest et al, 2015), their chances of developing infections with AMR strains is increasing year on year leaving many patients vulnerable. Advice on systemic antibiotic treatment for wound care is readily available in many trusts whereas advice on the use of topical non-antibiotic treatment is less prescriptive and best practice statements help to supplement these shortfalls (Wounds UK, 2013).

THE ROLE OF WOUND BIOFILM IN AMR

It is accepted that biofilms play a role in non-healing wounds that may show signs of infection. An accurate diagnosis of the organism(s) causing genuine wound infection in these wounds can be problematic and often do not readily respond to systemic antibiotics (Malone et al, 2017). Biofilms have been shown to allow the horizontal spread of antibiotic resistance genes between the bacterial cells encased within them (Flemming et al, 2016) and their involvement in the development of resistance should not be overlooked. As both antibiotic-resistant strains and biofilm are found in non-healing chronic wounds it is essential that these inter-relationships are somehow interrupted using biofilm-based wound care and wound healing needs to occur without the need for systemic antibiotics. This type of approach should minimise further environmental spread of antibiotic-resistant pathogens (Bowler, 2018).

ANTIMICROBIAL STEWARDSHIP AND EFFECTIVE USE OF ANTIMICROBIAL AGENTS IN WOUND CARE

There is a perceived overuse/misuse of antibiotics in wound care, especially related to leg ulcers (Gürgen, 2014). This was proven in a study carried out on 105 patients from primary care referred to a hospital setting in Norway. 75.1% patients had received treatment with antibiotics before they were referred to the wound healing unit with 53.3% of patients treated with systemic antibiotics. The personnel at the wound healing unit agreed with the indication for antibiotic therapy in only one case (0.9%). However, the same unit also identified the need for systemic antibiotics in 5.4% of patients who had not received this treatment from primary health services (Gurgen, 2014). A recent study undertaken by interrogation of the Health Improvement Network data (THIN) showed that 16.4% of antibiotic prescriptions were for skin/wounds. Penicillins accounted for 50% of all prescriptions, followed by macrolides (13%), tetracyclines (12%) and trimethoprim (11%). Their conclusions were that in almost one-third of all prescriptions, no clinical justification was documented (Dolk et al, 2018).

A position paper on antimicrobial stewardship in wound care has been jointly produced by the European Wound Management Association (EWMA) and the British Society of Antimicrobial Chemotherapy (BSAC) to provide guidance for wound care practitioners on the appropriate use of systemic and topical antibiotics to ensure the safest and most clinically effective therapy for the management of infected wounds (Lipsy et al, 2016).

The overuse of systemic antibiotics in wound care needs to be addressed and antimicrobial stewardship is key to implementation of appropriate use. In addition, putting together competency frameworks involving the whole multidisciplinary prescribing team with support from an antimicrobial stewardship committee is essential for preventing and controlling infections and fully understanding AMR, antimicrobials, their modes of action, and the spectrum of action of antimicrobials and the mechanisms of resistance (Roberts et al, 2017).

Finally, the current use of topical antiseptics needs to be carefully monitored in order to prevent the development of resistance in this area (Roberts et al 2017). Understanding when and how topical antiseptics should be used to prevent infection and to reduce bioburden is essential for all wound care practitioners and how they can be used to reduce the spread of AMR is essential for all wound care practitioners. If biofilm-based wound care is adopted globally and topical antisepsis and debridement more widely used, then overuse of antibiotics should reduce and help with the global problem.

CONCLUSION

AMR is an issue that spans multiple areas and cannot be solved by any one solution. Nor is it an issue that any one country can address successfully by acting alone. Hence a multi-

disciplinary approach to solving the diverse issues and coordination among various countries is critical. Despite the worldwide attention to AMR, there are substantial limitations in our full understanding of the burden of AMR at the population level. Epidemiological studies on the impact of the stewardship initiatives will hopefully inform strategies for the detection, prevention and management of AMR. In wound care, surveillance is difficult as many of the chronic wounds harbour AMR organisms but the nature of chronic wounds negate sampling and thus surveillance of AMR in isolates. The introduction of a point of care device for accurate diagnosis of wound infection in both acute and chronic wounds may help in this area and allow appropriate sampling and subsequent treatment of these wound types.

Currently, with limited diagnostic tools, empirical antimicrobial treatment will have to continue, increasing the risk of AMR further developing in wound isolates. WUK

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