The changing face of bacterial infection over the past 20 years

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People with diabetic foot ulcers (DFUs) are at increased risk of foot infection due to neuroischaemia and hyperglycaemia, which causes damage to neutrophil function, lymphocyte function, the antioxidant system and humoral immunity. Antibiotics have been an essential tool in reducing limb- and life-threatening infections in the diabetic population. However, bacterial resistance to antibiotics has been increasing and over the past 20 years there has been little achieved in stopping this rise. The outcome, if not challenged now, will be disastrous for the general population and worse for those with diabetes.

The first effective antimicrobial agent, sulfonamidochrysoidine, was introduced in 1937, following its discovery by Gerhard Domagk. However, bacteria resistant to sulphonamides occurred within two years. It was not until 1939 that Howard Florey, Ernst Chain and Norman Heatley showed the usefulness of penicillin *in vivo*, 11 years after its discovery by Alexander Fleming. This led to the first large-scale military use of penicillin in June 1944, the D-Day invasion of Normandy. In 1943, streptomycin was discovered by Albert Schatz becoming the first antibiotic to show efficacy against tuberculosis. These two antibiotics were used during the Korean War, often together and as prophylaxis. However, a review of antibiotic use in 1951 showed multi-resistant bacteria in nearly all war wounds and was partly attributed to prophylactic use (Manring et al, 2009).

More recently, antibiotic resistance has been attributed:

- Lack of antibiotic regulation in human use (in some countries selling antibiotics over the counter)
- Poor infection control practices
- Overprescribing of broad spectrum antibiotics
- Increase in the number of high-risk patients
- Lack of rapid testing for infective bacterial species
- Inappropriate prescribing
- Use of antibiotics in agriculture
- Global travel
- Poor sanitation.

Some bacteria are naturally resistant to certain types of antibiotics. However, bacteria may also become resistant by a genetic mutation or by acquiring resistance from another bacterium in plasmid genes, 'free' genetic material and viral transfer.

The overuse of antibiotics has led to several countries becoming 'hotspots' for antibacterial resistance. The centre for Disease Dynamics, Economics and Policy has produced an interactive antibiotic resistance map, which can be found at: *https://resistancemap.cddep.org/*. However, bacterial resistance to antibiotics exists worldwide.

The top 18 drug-resistant bacterial threats to the United States were published in a report outlining concern to the Centres for Disease Control and Prevention in the USA in 2013. These included: *Clostridium difficile* (CDIFF), carbapenem-resistant *Enterobacteriaceae* (CRE), drug-resistant *Campylobacter*, extended-spectrum ß-lactamase producing *Enterobacteriaceae*, vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), drug-resistant *Streptococcus pneumoniae*, vancomycin-resistant *Staphylococcus aureus* (VRSA), erythromycin-resistant Group A *Streptococcus* (GAS) and clindamycin-resistant Group B *Streptococcus* (GBS). The number of drug-resistant bacteria is worrying and growing.

So what has happened to bacterial resistance in the past 20 years?

In 1998, The World Health Assembly (WHA) made a resolution to urge member states to "develop measures to encourage appropriate and cost effective use of antimicrobials, to prohibit the dispensing of antimicrobials without the prescription of a qualified healthcare professional, to improve practices to prevent the spread of infection and thereby the spread of resistant pathogens, to strengthen legislation to prevent the manufacture, sale and distribution

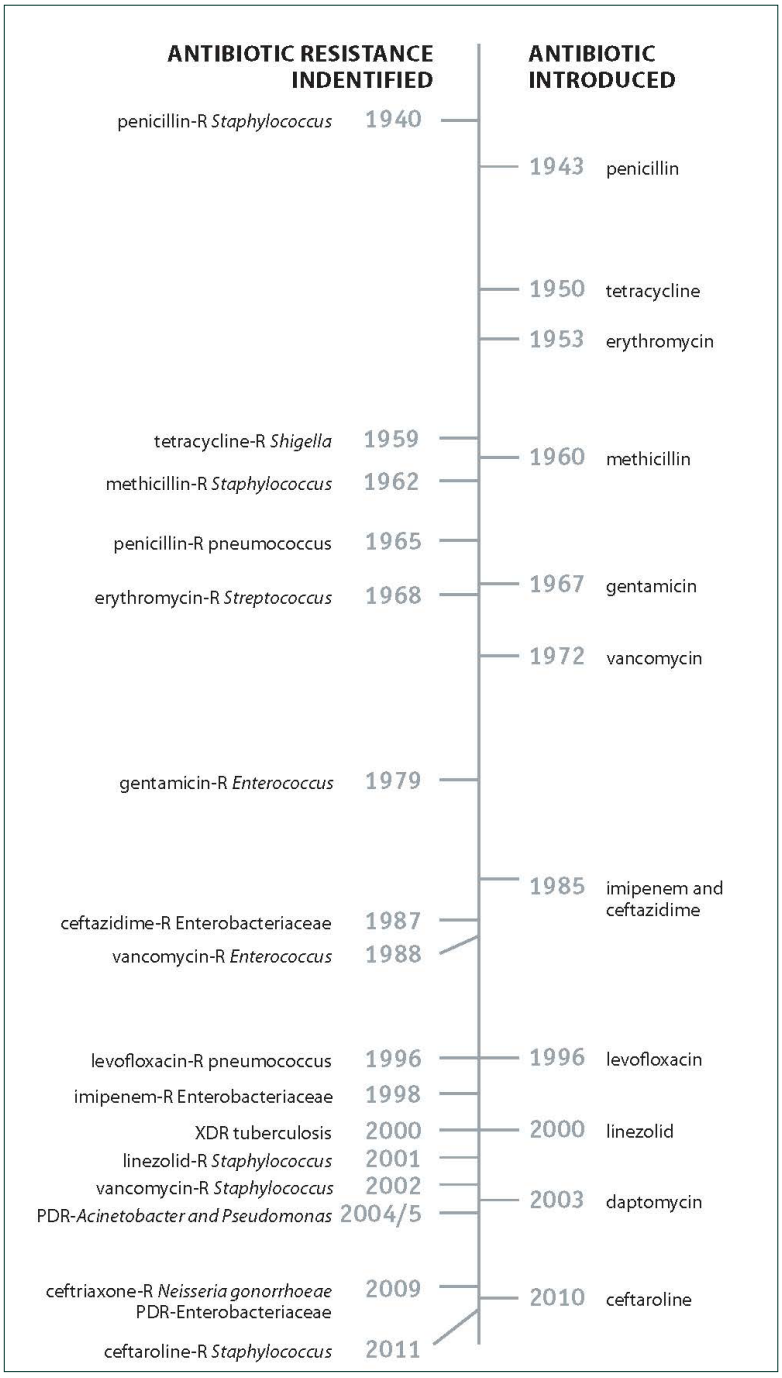

Figure 1. Antibiotic Resistance Threats in the United States, 2013 (Centers for Disease Control and Prevention, 2017).

of counterfeit antimicrobials and the sale of antimicrobials on the informal market, and to reduce the use of antimicrobials in food-animal production. Countries were also encouraged to develop sustainable systems to detect resistant pathogens, to monitor volumes and patterns of use of antimicrobials and the impact of control measures" (World Health Assembly, 1998).

In 2001, the World Health Organization published its *Global Strategy for Containment of Antibiotic Resistance* (WHO, 2001). This strategy encompassed the WHA's recommendations and went further to include education, regulation, management, guidelines and formularies, and surveillance of resistance for:

- Patients and the general community
- Prescribers and dispensers
- Hospitals
- Use of antimicrobials in food-producing animals
- National governments and health systems
- Drug and vaccine development
- Pharmaceutical promotion
- International aspects of containing antimicrobial resistance.

Finally, in 2013, the World Economic Forum included antibiotic resistance as a major 'global threat' to the world's economy. The report notes that: "Hubris on health not only means taking for granted that the technologies we have will continue to work, but also assuming that bigger and better scientific breakthroughs are just around the corner. There is no guarantee that putative alternatives to antibiotics will be developed before existing antibiotics become ineffective" (World Economic Forum, 2013).

A lack of new antibiotics

No new class of antibiotic has been introduced since 1993 (carbapenems). 'New' antibiotics, which have become available over the past 20 years, are analogues of the old classes of antibiotic. The analogues are made by adding an anti-bacterial resistance factor to the antibiotic, eg clavulanic acid added to amoxicillin to make co-amoxiclav. More analogues are in development, but bacteria will eventually become resistant to them, so they will only buy time in the fight against infection.

Only 3 of the 41 antibiotics in development have the potential to act against the majority of the most resistant bacteria. Therefore, a new class of antibiotic or mechanism for bacterial killing is required, preferably a drug that does not invoke resistance.

There are several reasons why pharmaceutical companies have not developed new classes of

antibiotic. It can take 10–15 years to get a new drug onto the market. The research and development costs can run into tens of millions of pounds, which the pharmaceutical company needs to make a return on investment and is prohibitive to many smaller pharmaceutical companies. However, the cost of antibiotics is low compared with other drugs, eg cancer treatments. Antibiotics are used short term and there is more financial gain in drugs for chronic conditions, e.g. statins. There is restraint in using the latest antibiotics, which tend to be used for the worst cases, e.g. linezolid was restricted by some NHS Trusts for life-threatening MRSA infections only. Also, resistance to a new analogue antibiotic is almost inevitable, therefore, reducing the use of the drug further.

However, the failure to address the problem of antibiotic resistance could result in an estimated 10 million deaths globally every year by 2050 at a cost of £66trn in lost productivity to the global economy.

What does the future hold?

We remain unable to identify if a bacterial colony will cause an infection in a wound. This problem along with finding a new class of antibiotic was raised as a challenge globally by the UK. In 2014, the public voted 'antibiotics' as the theme for the 'Longitude Prize', which can be found at: *https://longitudeprize.org/*. There are currently 239 teams competing from 41 countries. The Longitude Prize is looking to help tackle the problem of global antibiotic resistance with a £10m prize fund for a diagnostic tool that can rule out antibiotic use or help identify an effective antibiotic to treat infection.

Endolysins are enzymes produced by bacteriophages (bacterial viruses). The enzyme breaks open bacterial cell walls in order to release newly formed viruses and kills the bacteria in the process. Endolysins are specific to the type of bacteria they can interact with. They are also unlikely to cause bacterial resistance. A company in the Netherlands (Micreos) has produced a topical gel containing endolysin, which attacks *Staphylococcus aureus*. This is currently being trialled in patients with eczema to see if reduction of *Staphylococcus aureus* reduces the symptoms of eczema without affecting the skins normal 'biome'. However, there may be issues using endolysins systemically as they may cause a host immune reaction or release of bacterial endotoxins after cell wall lysis.

Most antibiotics have been produced by screening soil microorganisms for antimicrobial properties, but it has not been possible to cultivate 99% of these organisms in the laboratory. A team in the USA have developed an isolation chip (ichip) composed of several hundred miniature diffusion chambers and each chamber can be inoculated with a single environmental cell (Nichols et al, 2010). The ichip has been used to cultivate previously 'uncultivable' microbes. In 2015, a publication in *Nature* headlined 'A new antibiotic kills pathogens without detectable resistance' (Ling et al, 2015). The team of scientists from the USA had isolated a new species of proteobacteria provisionally named '*eleftheria terrae*'. This bacteria produced a compound not previously known — a depsipeptide — which the researchers named '*teixobactin*'. This compound inhibits cell wall synthesis causing autolysis and death of the bacterium. *In vitro* testing has so far shown no bacterial resistance to this compound, although the researchers admit that this may eventually occur. However, teixobactin may be the first step to understanding how antibiotic resistance can be prevented as the structure and function of the compound has recently been published (Parmar et al, 2017).

What can we do?

For those with DFUs, taking samples (preferably tissue) at the earliest stage of clinical signs of infection, before antibiotics have been started, is essential in targeting the infective bacteria with the narrowest range of antibiotic.

In a clinical setting, the simplest way to prevent infection spreading is through good clinical practice: hand washing, the cleaning of clinical areas, barrier nursing etc. It is also important that clinicians ensure the correct and efficacious use of antibiotics, guidelines for which have been published by NICE (2015): *Antimicrobial Stewardship: Systems and Processes for Effective Antimicrobial Medicine Use: NG15*.

As more allied health professionals are becoming independent non-medical prescribers, we should all be taking the pledge to become an 'Antibiotic Guardian'. This was a national call to action to "choose one simple pledge about how you'll make better use of antibiotics and help save these vital medicines from

becoming obsolete". You can make your pledge at: *http://antibioticguardian.com/*

Conclusion

There have been several analogues of antibiotics produced over the past 20 years, but no new classes of antibiotic have been introduced for human use in this time. The bacteria in soil remain a huge reservoir of potentially untapped antibiotics and new techniques are enabling scientists to grow them in large enough quantity to extract new compounds with antimicrobial properties that prevent resistance. Other natural killers of bacteria, such as bacteriophages, may also be a resource for creating antibiotics with no bacterial resistance. Clinic-based diagnostics are generally slow at identifying infectious bacteria and new techniques are required to ensure targeting of these species without the need to use broad spectrum antibiotics while waiting for results.

However, we cannot wait for new drugs to emerge as there is already a global crisis of increasing morbidity and mortality from multi-resistant bacteria. In patients with DFUs this is compounded as these infections are generally polymicrobial and already many ulcers contain multiple bacterial species with a variety of drug resistance.

So until we have new classes of antibiotics, we must also ensure good infection control in care settings, robust policies for antibiotic sustainability and promote disease prevention. Hopefully, we will see the emergence of new classes of antibiotic in the next 20 years and the fight against antibiotic resistant infection will go on. ■

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