Do we need to save antibiotics to save ourselves?

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Members of the health professions have had access to antibiotics for the last seventy years and medical advances are very dependent on them working effectively. However, there have been no new classes of antibiotics released in the last twenty years. There have been modifications to existing antibiotic classes and there is still a wide array of antibiotics available at this present time. But these numbers are reducing every year as bacteria become resistant. At some point their effectiveness may stop and we could be left without any antibiotics. Without antibiotic cover, the threat of infection and potential life threatening sepsis is high, especially when the patient is immunocompromised. Even simple infections can become complicated and result in cellulitis, loss of limb, loss of tissue, and sepsis if antibiotic treatment is not instigated at the right time.

The current higher-levels of antibiotic-resistant bacteria are attributed to the overuse and abuse of antibiotics. Antibiotic-resistant infections are often associated with hospitals and care settings, but recently antibiotic-resistant infections are now seen in the wider community too. We now have reports of antibiotic resistant tuberculosis, gonorrhoea, *Staphylococcus aureus (MRSA)* and extended spectrum beta lactamase (ESBL) Gram negative bacteria such as *Acinetobacter baumanii* or *Klebsiella pneumoniae*.

How can we stop the rapid development of antimicrobial resistance (AMR)? The recently commissioned review *Tackling Drug-resistant Infections Globally*, which was sponsored by the Wellcome Trust and the UK Department of Health (2016) and chaired by Jim O'Neill, has put forward nine interventions to reverse the situation. These are:

- 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.

This will not be an easy task and globally many countries are now looking at how these interventions can be initiated. In addition, research in alternative approaches to the prevention and treatment of infection including vaccination and bacteriophage therapy (viruses used to kill bacteria) is rapidly advancing but these approaches do not supersede antibiotics. We need to save our antibiotics to save ourselves and only allow their use when absolutely necessary. *Val Edwards-Jones*

1. What makes bacteria resistant to antibiotics?

KH: Antibiotics have a specific mode of action within the bacterial cell, involving a specific target site or multiple processes that are essential for bacteria to be killed. However, bacteria are capable of developing ways of overcoming a specific mode of action. This would be much more difficult if the antibiotics had multiple ways of killing bacteria. The abuse of antibiotics in clinical and veterinary practice is a major factor in the emergence of resistance and judicious use of these important drugs is essential to prevent a global catastrophe developing.

RW: As a precursor to answering all of these questions, it is implicit that clinicians recognize when bioburden is impacting wound healing, i.e. diagnose wound infection. This is a skill that comes with knowledge and experience. Scientifically, the mechanisms whereby selection for resistance occurs are very well known — and have been for quite some time. Practically, inappropriate use is the main reason. This includes numerous examples, such as use on viral infections, inadequate dosage, too short a duration of treatment, and many more. Not all may be attributed to clinician error; patients who do not complete the prescribed dose are also at fault. Antibiotics used in wound infections, usually in oral dosage forms, may select for resistance if the affected area (the wound and immediate environs) does not achieve the necessary therapeutic concentration of the drug. The

totally arbitrary oral dose of, for example 3 x 500 mgs antibiotic per day, does not ensure that, for reasons of local tissue perfusion, the infected wound tissues are adequately dosed. Similarly, where topical antibiotics are concerned, sensitivity, dosage and diffusion into the wound are all areas of concern. The use of antibiotics topically, where there are also systemic dosage forms of the same drug (e.g. Fucidin) is an area of particular concern when the selection for resistance is concerned. More research, and commonsense, are required in all such instances.

JM: Antibiotic resistance is when bacteria can begin to resist the effects of an antibiotic. This resistance occurs when bacteria change in a way that reduces the effectiveness of drugs. Every time a person takes them, sensitive bacteria are killed, but resistant bacteria may be left to grow and multiply. Inappropriate, non-targeted and over use of antibiotics are primary causes in resistance. Other causes are not finishing recommended courses, poor infection control and/or hygiene in health settings and the absence of new antibiotics being discovered to replace the increased resistant.

SW: Bacteria usually develop resistance to antibiotics in response to selection pressure. The presence of an effective antibiotic results in a selection pressure that selects for resistant strains. Random mutations that render bacteria resistant will allow that organism to survive and replicate while antibiotic sensitive strains will not survive within that population. The spread of genotypically resistant strains within a population establishes a resistant strain.

In addition to true genotypic resistance, bacteria can also demonstrate a decrease in susceptibility to antibiotics. This may be phenotypic rather than genotypic for example a bacterial species may alter their phenotype to produce a biofilm can offer both a physical and metabolic protection from antibiotic agents.

VEJ: The various classes of antibiotics have different modes of action, owing to the nature of their structure and degree of affinity to certain target sites within bacterial cells *(Table 1)*.

Table 1. Classes of antibiotics and their bacterial target site

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

Bacteria can be naturally resistant to some antibiotics because of their physical structure however, antibiotic resistance can be acquired through transfer of genes or genetic mutation.

There are four documented resistance mechanisms:

- 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, 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).

Any bacteria can acquire a single resistance gene or multiple resistance genes if conditions are optimal, allowing the collection of multiple resistance traits over time.

2. What happens when antibiotics stop working and what does this mean for the treatment of wound infections?

KH: It means that patients are exposed to increased risk of developing episodes of sepsis. This can make a patient very unwell and can even kill them so preventing the abuse of antibiotics is essential in modern day practice. In my opinion the major component of antibiotic stewardship that is not addressed is the education of clinical staff to ensure they do not use them unless there is good clinical evidence that they are required. The prescription of antibiotics or other antimicrobials based solely on a microbiological report should not be issued.

RW: If wound infection has been correctly diagnosed and, other compounding factors have been eliminated, then infection is the likely cause of delayed healing and/or wound deterioration. The clinical judgment to use antibiotics as a first choice intervention is questionable. The criteria justifying their use should be made clear. If they stop working there are a number of considerations, amongst which are:

- Change antibiotics
- Use topical antimicrobials either as an adjunct therapy or separately
- Check patient concordance with treatment
- Check for other diagnoses or relevant changes in health.

JM: When antibiotics stop working, the present and resistant bacteria will survive antibiotic treatment and continue to reproduce and mutate. It increases the risk of colonisation with resistant organisms which can also be transmitted to other patients. Diabetic foot ulcers have shown high levels of resistance already, in immunocompromised, diabetes, elderly patients, infection can spread quickly. For example, from a non-infected wound to a non-salvageable limb is not unknown. The reduction in effective antibiotics will be catastrophic in the

management of infection in these patients. Increased time of debility and associated health care costs as a result. Also, the global crisis is that there may be a time soon that antibiotics don't work at all and what was a minor infection is life-threatening.

SW: When antibiotics stop working clinicians look towards alternative antibiotics, increased duration or concentration of antibiotics and/or antibiotic cocktails to treat resistant bacterial populations. In more troubling scenarios organisms can lack susceptibility to multiple antibiotics. This scenario contributes to long-term chronic wounds that display stalled healing due to chronic inflammation. In situations where no alternative to antibiotics can be found, persistent, untreatable wound infections can lead to amputation and sometimes death.

VEJ: It is estimated that unless action is taken now, deaths from AMR infection could balloon to 10 million lives each year by 2050, at a cumulative cost to global economic output of 100 trillion USD (Wellcome Trust and Department of Health, 2016). As available antibiotics stop working, the risks of acquiring infection become higher. During any medical procedures where antibiotics are essential for a positive outcome (e.g during cancer chemotherapy or a bone marrow transplant), the treatments will leave the patients exposed to bacterial infections. If they acquire antibiotic-resistant infections, then the available treatments will be very limited. Patients in high-dependency facilities can experience high rates of infection as a result of the interventions that they receive.

Patients with wound infection face similar problems. Many of the common wound pathogens seen in acute and chronic wounds are already resistant to many antibiotics, making their treatment very difficult. Patients with resultant osteomyelitis or cellulitis require antibiotics to save limbs or prevent infection spreading into the bloodstream and resultant sepsis. If antibiotics do not work effectively for this group of patients, their treatment will become compromised and more serious complications result.

3. What can we do to tackle the problem?

KH: Carefully assess whether the wound needs treatment. Ensuring an appropriate drug at an effective dose given for the shortest period of time to be effective. Consider the use of non-antibiotic antimicrobials, if there is no evidence of spreading infection. Accept the quality of evidence to justify use of such agents is not as high as it should be. Do not prescribe an antimicrobial just in case.

RW: When wound infection is diagnosed, or strongly suspected, decide whether to use topical antimicrobials such as silver, PVP-iodine, honey etc or antibiotics as first-line intervention. Systemic antibiotics may not always be the logical first choice. Topical antibiotics are rarely justified for such use. Use systemic antibiotics sparingly, according to the published standards and criteria for antibiotic stewardship.

JM: Antimicrobial stewardship aims to govern the use of antibiotics. The chain in transmission of infection should be considered as can be distorted by infection control techniques:

- Aseptic techniques
- Hand hygiene
- Appropriate equipment.

Direct and local antibiotic considerations:

- Not overusing and consider other approaches as first line and support the reduction of side effects, such as *C-difficile*
- Directing antibiotics to specific organisms and levels of infection, i.e. tissue, bone
- Close monitoring of wound and monitor bloods for variance
- Deep swabbing and tissue sampling where possible
- Familiarising with 'local' bacteria as geographical areas can vary and local guidelines for antibiotic use in specific wounds
- Regular discussion the microbiology department
- No ability to buy over the counter antibiotics.

SW: In terms of wound healing there are a number of alternate options, such as wound dressings that are impregnated with antimicrobials, which can be used as an addition to systemic antibiotics. Even multidrug-resistant bacteria can be treated using appropriate antimicrobial agents. The problem with this strategy alone is that antimicrobial wound dressings typically require direct contact with the organism of interest, thus they do not typically address systemic infections or resistant organisms that are able to reside deeper within the wound.

Other treatments, such as wound debridement, can help to physically remove resistant populations and an increasing number of medical devices such as UV and electrostatic devices claim to be able to treat resistant populations. As with wound dressings, these devices do not claim to treat systemic infections.

VEJ: We need to do a number of things at a global level to tackle this problem and one of the first is to reduce current antibiotic consumption by reducing unnecessary usage in humans, animals, agriculture and the environment. Preserving the effectiveness of existing and new drugs is essential. It is very important that the recommendations of the AMR report are acted upon and that global public awareness is markedly improved. Hygiene needs to be improved and we now need to focus on prevention of infection and improve infection control and its spread. More surveillance is essential and it was not until mandatory surveillance was introduced that we realised how widespread the problem was. It would be useful to be able to diagnose infection using appoint of care device instead of waiting for the full diagnosis form the laboratory. A point of care device for accurate

diagnosis of wound infection would really help reduce the unnecessary use of antibiotics.

People living with chronic wounds often have numerous courses of antibiotics prescribed because the patient often has a sub-clinical infection, sometimes pathogens may be present without causing overt infection. Antibiotics often do not resolve the problem because a biofilm is present in chronic wounds and levels needed to eradicate a biofilm is higher than those reached in tissue or the bloodstream. Biofilm based wound care is now advocated by wound care professionals, using cleansing, debridement and topical antiseptics instead of unnecessary antibiotics. It is very important to note that this is not the case for acute wound infection where accurately targeted antibiotics will frequently resolve the infection in a few days.

Sometimes there is raised concern about the development of antiseptic resistance (for example silver) and although silver resistant genes have been described there have been no isolates observed clinically. This is not the same for all antiseptics, and close monitoring of antiseptic susceptibility should be undertaken alongside antibiotic susceptibility to ensure that the same scenario does not occur for antiseptics.

4. Are new antibiotics the only way to solve this problem?

KH: New antibiotics are not the answer, as unless these drugs have multiple modes of action, the problem of resistance is likely to develop again. Education of staff, prevention of infection and targeted antibiotic use are all components of effective and professional care of patients. The creation of local networks of clinicians with an expertise in this area is essential to set up local guidelines that can be effectively monitored and updated as required.

RW: Without doubt new antibiotics will be essential and the sooner, the better. We are reliably informed that the 'post-antibiotic age' is upon us. This is a common theme throughout medicine and not at all exclusive to wounds. Realistically, these new drugs are not going to be available in the short term as new ones take about a decade to bring to market. In the meantime, the measures outlined in my earlier responses will be important.

It is also essential to advise on the value and use of topical antimicrobials. Their use in the management of wound infection has a long history: for example Lister used phenol for such purposes. Agents such as honey, enzyme alginogel, iodine (as PVP-iodine), silver, biguanides, etc have been widely used in wound bioburden control. However, not all are known to have activity against organisms in biofilm colonies. Honey (Manuka) and enzyme alginogel are two agents which have 'anti-biofilm' activity. Published evidence strongly suggests that, correctly selected and used, topical antimicrobials can be of considerable value in managing wound infection.

Our understanding of antimicrobial peptides and the advent of one such, LL-37, promises much for the future. These agents are integral parts of the innate immune system and have evolved over millennia, hence selection for resistance is not likely to be an issue.

JM: No, the development of new antibiotics will not be the saviour to these issues. It is unlikely we will ever be free of resistance. The introduction of new antibiotics will likely result in overuse and it will become resistant unless the behaviours of prescription, administration and taking the drugs are changed. Stewardship being implemented will support the delay of resistance but it won't stop it completely.

SW: The development of new antibiotics is one response to the issues relating to antibiotic resistant bacteria. However, other options include altered treatment regimens using current antibiotics, improved and more targeted antibiotic treatments relating to personalised care and combination treatments that incorporate physical debridement, wound irrigation, antimicrobial treatments and appropriate antibiotic use. Ultimately, the best patient treatments and the lowest risk for the development of antibiotic resistant strains are likely to stem from an improved understanding and targeted treatments.

VEJ: We do need more antibiotics where resistance is on the rise. Supply of new antibiotics is expensive and many pharmaceutical companies invest in more profit making drugs rather than antibiotics because of costs associated with their discovery and implementation. A pipeline of new antibiotics is not forthcoming and we need to protect the antibiotics we have to prevent further development of AMR, especially in common pathogens. More investment is needed in order to produce new antibiotics and this is slowly becoming available to both research academics and commercial companies. We need to protect the antibiotics we have as well as produce new ones.

Infection in the vulnerable population should be prevented wherever possible by making the environment as hygienically clean as possible. Minimum invasive procedures should be adopted wherever possible and all materials implanted into patients should be made of materials which prevents biofilm formation and development of local infection.

Wounds should be cleaned and dressed with materials that deter bacteria and if infection does occur then a POC test should confirm this and the wound targeted with specific spectrum antibiotics.

Treatment of the waste from an infected patient (solid, fluids and materials contaminated with them) should be tightly monitored and AMR spread stopped wherever possible.

In summary, there are alternative approaches that could be instigated to help prevent infection developing and we as a wound care community should be looking at practices that reduce the need and use of antibiotics in wound care. WUK

REFERENCES

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