

Antimicrobial resistance relating to wound management and infection

Sussman G

ABSTRACT

Antimicrobial resistance is now a global threat. Its emergence rests on antimicrobial overuse in humans and food-producing animals; globalisation and suboptimal infection control facilitate its spread. While aggressive measures in some countries have led to the containment of some resistant Gram-positive organisms, extensively resistant Gram-negative organisms are pan-resistant. The achievements of modern medicine are put at risk by antimicrobial resistance. Without effective antimicrobials for prevention and treatment of infections, the success of organ transplantation, cancer chemotherapy and major surgery would be compromised. Inappropriate use of antimicrobials drives the development of drug resistance. Both overuse, underuse and misuse of medicines contribute to the problem. The Australian government has launch Australia's First National Antimicrobial Resistance Strategy; however, without urgent, coordinated action, the world is heading towards a post-antibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill.

INTRODUCTION

What is antimicrobial resistance? The evolution of resistant strains is a natural phenomenon that occurs when microorganisms replicate themselves erroneously or when resistant traits are exchanged between them. The use and misuse of antimicrobial drugs accelerates the emergence of drug-resistant strains. Poor infection control practices, inadequate sanitary conditions and inappropriate food handling encourages the further spread of antimicrobial resistance. Why is antimicrobial resistance a global concern? New resistance mechanisms emerge and spread globally, threatening our ability to treat common infectious diseases, resulting in death and disability of individuals who until recently could continue a normal course of life. Without

effective anti-infective treatment, many standard medical treatments will fail or turn into very high risk procedures.

Antimicrobial resistance is now a global threat. Its emergence rests on antimicrobial overuse in humans and food-producing animals; globalisation and suboptimal infection control facilitate its spread. While aggressive measures in some countries have led to the containment of some resistant Gram-positive organisms, extensively resistant Gram-negative organisms such as carbapenem-resistant Enterobacteriaceae and pan-resistant *Acinetobacter* spp. continue their rapid spread¹.

The WHO's 2014 report on global surveillance of antimicrobial resistance reveals that antibiotic resistance is no longer a prediction for the future; it is happening right now, across the world, and is putting at risk the ability to treat common infections in the community and hospitals. Without urgent, coordinated action, the world is heading towards a post-antibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill².

Antimicrobial conservation/stewardship programs have seen some measure of success in reducing antimicrobial overuse in humans, but their reach is limited to acute-care settings in high-income countries. There is scant or no oversight of antimicrobial administration to food-producing animals, while evidence mounts that this administration leads directly to resistant human infections.

Microbial resistance is emerging faster than we are replacing our armamentarium of antimicrobial agents. Resistance to penicillin developed soon after it was introduced into clinical practice in 1940s. Now resistance developed to every major class of antibiotics. In health care facilities around the world, bacterial pathogens that express multiple resistance mechanisms are becoming common. The origins of antibiotic resistance genes can be traced to the environmental microbiota. Mechanisms of antibiotic resistance include alterations in bacterial cell wall structure, growth in biofilms, efflux pump expression, modification of an antibiotic target or acquisition of a new target and enzymatic modification of the antibiotic itself. Mechanisms of resistance in the biofilm include increased cell density and physical exclusion of the antibiotic. The individual bacteria in a biofilm can also

Geoff Sussman

OAM JP FPS FAIPM FACP FAWMA,
Associate Professor
Faculty of Medicine, Nursing and Health Sciences,
Monash University, Vic, Australia

undergo physiological changes that improve resistance to biocides.

Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness, higher health care expenditures, and a greater risk of death. As an example, the death rate for patients with serious infections caused by common bacteria treated in hospitals can be about twice that of patients with infections caused by the same non-resistant bacteria. For example, people with MRSA (methicillin-resistant *Staphylococcus aureus*, another common source of severe infections in the community and in hospitals) are estimated to be 64% more likely to die than people with a non-resistant form of the infection³.

When infections become resistant to first-line drugs, more expensive therapies must be used. A longer duration of illness and treatment, often in hospitals, increases health care costs as well as the economic burden on families and societies. For example, Vancomycin 500 mg vial \$1.50/week \$42.00 Linezolid 600 mg vial \$143.75/week \$2012.50. The achievements of modern medicine are put at risk by antimicrobial resistance. Without effective antimicrobials for prevention and treatment of infections, the success of organ transplantation, cancer chemotherapy and major surgery would be compromised. Inappropriate use of antimicrobials drives the development of drug resistance. Both overuse, underuse and misuse of medicines contribute to the problem. Many infectious diseases may one day become uncontrollable. With the growth of global trade and travel, resistant microorganisms can spread promptly to any part of the world.

Ensuring that patients are informed about the need to take the right dosage of the right antimicrobial requires action from prescribers, pharmacists and dispensers, the pharmaceutical industry, nurses, the public and patients, as well as policy makers.

Surveys of antibiotic use in hospital and community settings show that a third to a half of all prescriptions are discordant with widely available antibiotic guidelines. Individual decisions to prescribe are often driven by the prescriber's experience, confidence and tolerance of risk, rather than by objective clinical indications. Antimicrobial stewardship programs are designed to support and share responsibility for logical, evidence-based antibiotic prescribing decisions in the context of inevitable clinical uncertainty, and they can reduce unnecessary — and overall — antibiotic use, without adverse patient outcomes⁵.

Dr Evan Ackermann, chair of the Royal Australian College of General Practitioners national standing committee for quality care, said priority should go to antibiotic stewardship programs in general practices to ensure antibiotics were being prescribed "at the right time, for the right reason, and to reduce poor prescribing and adverse events"⁶.

Infection of foot ulcers is a common, often severe and costly complication in diabetes. Many factors linked to the host, mainly immune defects, neuropathy and arteriopathy, as well as bacteria-related factors, interact in a complex way and account for the susceptibility of diabetic individuals to foot infections, the severity of such infections and difficulty to treat them³. Due to the frequent infections or recurrences, the diabetic patients have more exposure to antibacterial agents. Immunocompromised state and frequent antibiotic use are associated with antibiotic resistance of the causative agents of the infections in these patients, such as methicillin-resistant *S. aureus*, *Streptococcus pneumoniae*, Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, bacteria in diabetic foot infections, and involvement of different opportunistic and rare pathogens or multidrug-resistant strains in the infections².

A study was designed to examine the bacteriological and resistance profile of isolates obtained from diabetic patients. In all, 38 of 125 diabetic patients (30.4%) had bacterial infection *Escherichia coli* among Gram-negative bacteria and *S. aureus* among Gram-positive bacteria were the predominant pathogens. Methicillin resistance was found in 50%. Resistant bacterial infections in diabetic patients are common⁴.

In the context of increasing resistance to antibiotics and the dramatic fall in the number of antibiotics in development, restriction of other potentially useful antimicrobial treatments such as silver dressings is particularly unfortunate. Topical antiseptics, such as silver, differ from antibiotics: they have multiple sites of antimicrobial action on target cells and therefore a low risk of bacterial resistance. As a result, antiseptics have the potential to play an important part in controlling bioburden in wounds while limiting exposure to antibiotics and reducing the risk of development of further antibiotic resistance.

Topical antibiotics should only be used in infected wounds under very specific circumstances by experienced clinicians. Topical metronidazole gel might be used for the treatment of malodour in fungating wounds, silver sulphadiazine in burns, and in wounds mupirocin, a specific topical antibiotic with no similar compounds, can be used systemically or orally. Chloramphenicol ophthalmic ointment is widely used by plastic surgeons as topical surgical prophylaxis postoperatively. The application of a single dose of topical chloramphenicol to high-risk sutured wounds after minor surgery produces a moderate absolute reduction in infection rate that is statistically but not clinically significant⁷. A theoretical but as yet not conclusively proved risk of chloramphenicol-induced idiosyncratic aplastic anaemia exists with topical ophthalmic therapy. In the UK in the past 10 years, 11 reports (all non-fatal) of suspected topical chloramphenicol-induced blood dyscrasia have been reported⁸.

A Norwegian study by Gürgen suggest a significant excess use of antibiotics in patients with non-healing ulcers. Mounting evidence suggests that the use of antibiotics should be reduced significantly among this population because antibiotics do not treat the underlying cause of the ulcer. A reduction of antibiotic use among this patient population will significantly reduce antibiotic resistance and health care costs associated with the side effects of antibiotics⁹.

A study by Öien *et al.* investigated changes in ulcer healing time and antibiotic treatment in Sweden following the introduction of the Registry of Ulcer Treatment (RUT), a national quality registry, in 2009. According to the adjusted registry in December 2012, patients' median age was 80 years (mean 77.5 years, range 11–103 years). The median healing time for all ulcers, adjusted for ulcer size, was 146 days (21 weeks) in 2009 and 63 days (9 weeks) in 2012 ($p=0.001$). Considering all years between 2009 and 2012, antibiotic treatment for patients with hard-to-heal ulcers was reduced from 71% before registration to 29% after registration of ulcer healing ($p=0.001$). The conclusions were that healing time and antibiotic treatment decreased significantly during the three years after the launch of the RUT¹⁰.

The Australian Government has launch Australia's first National Antimicrobial Resistance Strategy 2015–2019¹¹. Its aims include:

1. Increase awareness and understanding of antimicrobial resistance, its implications and actions to combat it, through effective communication, education, and training.
2. Implement effective antimicrobial stewardship practices across human health and animal care settings to ensure the appropriate and judicious prescribing, dispensing and administering of antimicrobials.
3. Develop nationally coordinated One Health surveillance of antimicrobial resistance and antimicrobial usage.
4. Improve infection prevention and control measures across human health and animal care settings to help prevent infections and the spread of resistance.
5. Agree a national research agenda and promote investment in the discovery and development of new products and approaches to prevent, detect and contain antimicrobial resistance.
6. Strengthen international partnerships and collaboration on regional and global efforts to respond to antimicrobial resistance.
7. Establish and support clear governance arrangements at the local, jurisdictional, national and international levels to ensure leadership, engagement and accountability for actions to combat antimicrobial resistance.

All health professionals working in health and, in particular, in wound care have a responsibility to ensure the appropriate use of antibiotics. The general principles are:

- Use Antibiotic Therapeutic Guidelines when prescribing antimicrobials.
- Local guidelines should take into account recommendations in Antibiotic Therapeutic Guidelines and also reflect local antimicrobial susceptibilities.
- Consult the best available evidence and specialist clinicians for guidance on the management of infections not covered by guidelines.
- Ensure guidelines are readily accessible wherever antimicrobials are prescribed.
- Confirm the presence of infection.
- Identification of the pathogen.
- Selection of therapy.
- Monitor therapeutic response.

Practise antibiotic stewardship to model an understanding of the risks and benefits. While it takes more time to teach the patient and family about the hazards of antibiotics, it may be education that can be reinforced by nurses or written material provided to the patient¹². Patients may also express more satisfaction when they are carrying a written prescription, rather than "allowing the body to heal itself"¹³. However, chronic wounds may not improve with antibiotics unless biofilm is removed.

The misuse of antibiotics for trivial infections, as well as inappropriate and excessive use arising from access to antibiotics by non-specialists in over-the-counter sales has contributed to the emergence of antibiotic resistance. Therefore ways to promote the better use of antibiotics include restricting their use to appropriate circumstances, which involves selecting the pertinent antibiotic for each case, using it only when needed, at the right dose and for the correct period. It also depends on using authentic antibiotics, rather than fake or adulterated ones. Appropriate antibiotic stewardship requires global consensus to devise suitable decision pathways, treatment guidelines and regulatory mechanisms to reduce antibiotic selective pressures¹⁴. The International Wound Infection Institute has published the Ten Top Tips reducing antibiotic resistance and they are a useful guide¹⁵.

Infection will continue to be a problem with wounds. Complicating the issue is the increased resistance to antibiotics and the lack of development of new antibiotics. Antiseptics play an important role in reducing bioburden and as an antimicrobial barrier. It is essential to understand when they are appropriate and how best and for how long to use them.

REFERENCES

- Huttner A, Harbarth S, Carlet J *et al.* Antimicrobial resistance: a global view from the 2013 World Healthcare-Associated Infections Forum. *Antimicrob Resist Infect Control* 2013;2:31.
- World Health Organization. Antimicrobial Resistance Global Report on Surveillance 2014. Available from: <http://www.who.int/drugresistance/documents/surveillance-report/en/>
- Diabetes Metab Res Rev* 2012;28(Suppl 1):46–53.
- Bacteriological and resistance profile in isolates from diabetic patients. *N Am J Med Sci* 2012 Nov;v4(11).
- Gilbert GL. Knowing when to stop antibiotic therapy. *Med J Aust* 2015;202(3):121–122.
- Evan Ackermann E. *MJA Insight* Nov 2015.
- Heal CF, Buettner PG, Cruickshank R *et al.* Does single application of topical chloramphenicol to high risk sutured wounds reduce incidence of wound infection after minor surgery? *BMJ* 2009;338:a2812.
- Doona M, Walsh JB. Use of chloramphenicol as topical eye medication: time to cry halt. *BMJ* 1995;310:1217.
- Gürgen M. Excess use of antibiotics in patients with non-healing ulcers. *EWMA J* 2014;v14(1):17–22.
- Öien RF, Forssell HW. Ulcer healing time and antibiotic treatment before and after the introduction of the Registry of Ulcer Treatment: an improvement project in a national quality registry in Sweden. <http://bmjopen.bmj.com/> accessed 28 April 2015.
- National Antimicrobial Resistance Strategy 2015–2019 ISBN: 978-1-76007-191-2 Online ISBN: 978-1-76007-192-9.
- Hertz BT. Easing the strain of unnecessary antibiotic requests. Physicians called on to change patient expectations about antibiotic use; experts say it's about communication. *Med Econ* 2014 Jan 10;91(1):32–5.
- Shapiro E. Injudicious antibiotic use: an unforeseen consequence of the emphasis on patient satisfaction? *Clin Ther* 2002;24(1):197–204.
- World Health Organization (2011). WHO Global strategy for the containment of antimicrobial resistance. http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf?ua=1 accessed 4 November 2014.
- Sussman G, Swanson T, Black J, Cooper R, Schultz G, Fletcher J, Smith D. Ten top tips: reducing antibiotic resistance. *Wounds Int* 2014; 5(4):4–8.

REDUCTION IN CHRONIC WOUND PAIN REDUCTION OF BACTERIAL BURDEN¹

KENDALL™ AMD ANTIMICROBIAL FOAM DRESSINGS WITH PHMB (POLYHEXAMETHYLENE BIGUANIDE HCl)

Results of the trial suggests PHMB impregnated foam dressing as a viable option for the treatment of critically colonised chronic wounds.

¹: Sibbald RG, *et al.* *AdvSkin Wound Care* 2011;24(2): 78-84



Covidien Pty Ltd. A Medtronic company. 166 Epping Road Lane Cove, NSW 2066. P: +61 2 9429 3100
Covidien New Zealand Ltd. A Medtronic company. 666 Great South Road, Penrose, Auckland 1051 P: +64 9 967 4600
www.medtronic.com.au © 2015 Medtronic. All Rights Reserved WC 193-08-15

Medtronic