Ten top tips: reducing antibiotic resistance

The World Health Organization (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 now, across the world[1]. This has been driven by antibiotic overuse in humans and food-producing animals, globalisation, and suboptimal infection control. Underuse and misuse of medicines also contribute to the problem, and sub-therapeutic doses of antibiotics used in animal-rearing can result in resistant microorganisms, which can spread to humans[1].

Resistance to penicillin developed soon after it was introduced into clinical practice in the 1940s. Resistance has now developed to every major class of antibiotics. Bacterial pathogens that express multiple resistance mechanisms are becoming common around the world. 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. The death rate for patients with serious infections caused by common bacteria treated in hospitals can be twice that of patients with infections caused by the same non-resistant bacteria[2].

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 spread. Microbial resistance is emerging faster than we are replacing our armamentarium of antimicrobial agents. Therefore 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[2]. These top ten tips provide a summary of the key points considered at an international level as priorities to contain and minimise the spread of antibiotic resistance.

**BACKGROUND**

Antimicrobials are agents that inhibit the growth of or kill micro-organisms, and they fall into four categories:

- **Antibiotics:** Active against bacteria and predominately given systemically for wound infections. Antibiotic resistance can be defined as the ability of bacteria to overcome the effect of antibiotic medicines
- **Anti-fungal agents:** Active against fungi
- **Antiviral agents:** Active against viruses
- **Anti-parasitic agents:** Active against parasites.

There are also other broad spectrum antimicrobial agents, such as antiseptics, disinfectants, preservatives and biocides (which are chemically derived but applied topically). Antiseptics are chemical, broad-spectrum, antimicrobial agents which can be applied topically to skin or underlying tissues to prevent/control infection and increasing bacterial colonisation, by killing or inhibiting pathogens.

1. **Develop new treatments**

For almost 20 years, no new classes of antibiotics have been discovered, and only variations of existing drugs have been developed. With the emergence of so many multiresistant bacteria there is an urgent need for new strategies which target broader microbial targets than the specific biosynthetic pathways targeted by antibiotics, in order to reduce the selective pressures that drives resistance. Bacteriophages are a diverse group of viruses which are easily manipulated, and therefore have potential uses in therapeutics[1]. Bacteriocins are proteinaceous toxins that are produced by bacteria to inhibit the growth of other bacterial strains. They are typically considered to be similar to narrow-spectrum antibiotics, and the approximately 30 bacteriocins that have been identified are structurally and functionally diverse[6]. Natural and synthetic inhibitors of the quorum-sensing systems are being developed that can reduce the conversion of single, planktonic bacteria into attached biofilm communities that impair healing of wounds. Combining quorum-sensing inhibitors with conventional antibiotics would greatly enhance their microbicidal activity in chronic wounds that contain biofilm and planktonic bacteria.

However, pharmaceutical companies tend to pursue more profitable causes than the development of new antibiotics. It is understandable when the expenditure required for research and development in a commercial environment is significant and it has been demonstrated that resistance to a...
new antimicrobial is likely to emerge within a foreseeable timeframe, rendering the new product less marketable. For these reasons funding needs to be provided by governments to encourage industry to recommence this type of research. Another reason for the lack of new antibiotic development is the length of time needed to obtain regulatory approval to bring a new product on to the market. Regulatory bodies will therefore need to develop safe fast-track approval systems for new antibiotics.

2 Provide education to prescribers and consumers on the benefits of judicious use of antimicrobial agents in wound care

Formal education on the benefit of limited use of topical antibiotics for the treatment of chronic wounds should be based on available guidelines, such as the Australian therapeutic guidelines for antibiotics. These documents are well respected and can serve as an unbiased guide for care. Education should be targeted at all levels, including governments and the public as well as health professionals.

As well as providing knowledge and skills, education should aim to change attitudes about antibiotics in wound care. Prescribers of antibiotics are trained to be cautious of missing serious treatable disease, and this cautious attitude may tip the balance in favour of giving antibiotics. In addition, in terms of liability, while many healthcare professionals may know of someone who has been sued for missing bacterial disease, no-one has ever been sued because they contributed to antibiotic resistance. Documenting the reasons for not using antibiotics will be helpful if litigation occurs.

Patients may expect antibiotics as part of a treatment programme and may also express more satisfaction when they are given a written prescription. Therefore, any change must begin at the provider-patient interface where the appropriate use of antibiotics can start. Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials. This approach is universally accepted as best practice and should be practised to model an understanding of the risks and benefits. Teaching and reinforcement by all healthcare professionals, as well as provision of written material, can help patients and families understand the hazards of antibiotics. It must be remembered that in some cases, chronic wounds may not improve with antibiotics unless biofilm is removed.

3 Develop faster methods of identifying wound infection

One of the drivers of antibiotic overuse is the time taken for a pathology report on a swab or biopsy to identify the presence of and the sensitivity of infecting bacteria. New and rapid methods are required to accurately identify infection using DNA and biomarkers for example. Once proven accurate for best results, it is likely that these methods will need to be funded by government reimbursement schemes.

4 Use conservation programmes to address inappropriate use of antimicrobials

Since the use of low antibiotic doses in animal feed for animal growth enhancement began, there have been concerns that increasing resistance would alter the effectiveness of therapeutic antibiotics for humans. The emergence of glycopeptide-resistant enterococci in 1993 led to a European ban on antibiotic animal growth promoters that were used in treating human infections, and the use of remaining antibiotic feed additives was prohibited from the 1st January 2006. However, this non-medicinal use has allowed the presence of antibiotic residues in foods, and increased antibiotic-resistant strains in animals, with the subsequent possibility of transfer to humans across continents. Yet antimicrobial growth promoters are still used in some non-European countries, and antibiotics continue to be employed in treating animal infections. Animal infections should be treated with antibiotics not used in humans and animal growth-promoting antibiotics should be banned. The effects of discontinuing animal growth promoters in animal production and banning prophylactic antibiotic use in pigs has been shown to reduce resistance levels.

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. Antibiotic use should be restricted 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 requires the use of 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 pressures.
12. 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; 91(1):32–5

By closely monitoring antibiotic-resistant bacteria at a local, national and international level it is possible to determine the extent of the threat of failure to effectively treat infections. Hence control strategies can be formulated rationally, antibiotic resistance reservoirs can be identified, suitable containment plans can be generated and appropriate resources can be calculated. Although many countries have efficient surveillance programmes, more widespread monitoring, better communication and coordination on a global scale is needed if antibiotic resistance is to be controlled.

5 Develop and follow policy
Controlling antibiotic resistance requires a multi-pronged approach. Many of the latest guidelines recommend both better hygiene and infection control practices to prevent infection, and appropriate prescribing of antibiotics. Common areas that provide guidance on managing infection, while preventing resistance, include:

■ Promoting best practice in antibiotic prophylaxis and therapy; through use of guidelines for antibiotic therapy, surgical prophylaxis, and intravenous-to-oral switch; as well as formulary use (the traffic light approach)
■ Better use of resources by using cheaper but equally effective drugs where possible. This can be achieved through antibiotic committees, and regular audits and data collection
■ Decreasing the emergence and spread of antibiotic-resistant bacteria, through both stewardship and microbiology ward rounds, infection control practices and automatic stop policy (where the prescriber provides a stop/review date and indications for prescription)
■ Improving education of potential/ future prescribers by providing guidelines on appropriate therapy
■ Restricting use of unnecessary or ineffective antibiotics and use of expensive or unnecessarily powerful ones
■ Improving consumer knowledge and expectations regarding antibiotics. The 2013 Cochrane Collaboration concluded that interventions such as those stated above can be effective in reducing antibiotic resistance. However, while most guidance is aimed at hospital institutions, most antibiotics are prescribed in the community. Therefore more guidelines are required for primary care providers.

6 Ensure facility cleaning and waste storage
Recommendations regarding cleaning of facilities where patient care is provided include the following:
■ Frequently touched surfaces should be cleansed daily with a detergent solution when visibly soiled and after every known contamination
■ All shared equipment should be cleansed with a detergent solution between patient uses
■ Use of surface barriers, such as waterproof sheeting, to protect clinical surfaces including equipment which is difficult to clean, likely to become contaminated with blood or body surfaces or touched frequently with gloved hands during the delivery of patient care
■ Local decontamination procedures should be adhered to for blood or potentially infectious materials
■ All organisations should have a roster of duties and frequency of cleaning. Staff members should understand their responsibilities and the correct use of products required for a variety of scenarios
■ All cleansing and disinfectant products should be approved for use and used according to manufacturer’s instructions
■ All carpets in public and general areas should be vacuumed daily and any spills removed using a hot water extraction method. General cleaning should occur on a regular basis using a method that minimises the production of aerosols
■ Local and national cleaning standards should be applied and audited for compliance.

The World Health Organization has reiterated their concerns about soil and water environments as sources for antibiotic resistant genes. Management of manure is an important component as composting eliminates on average 50–70% of some antibiotics, but other strategies include prevention of lagoon spills and seepage, control of surface run-off, limiting sediment erosion and management of animal transportation. Domestic, hospital and industrial waste water treatments are also areas where recommendations have been noted.

Areas of promise include thermophilic anaerobic sludge digestion, incineration, containment and monitoring of outflow.

7 Adopt management strategies for infected wounds
Antibiotic-resistant organisms may be present from the beginning of a wound’s development. Control of a wound’s...
bacterial load is pivotal to effective wound healing[27]. Progression along a continuum from contamination to colonisation, to critical colonisation (pre-infection), to local wound infection, to deep spreading infection (cellulitis and lymphangitis) to septicemia and multi-organ failure and death, can occur if bacterial burden management strategies are not implemented in a timely manner. The presence of bacterial biofilm must be considered in all non-healing chronic wounds[15].

All wound care must be performed using a high standard of infection control and prevention principles to prevent cross contamination of patients’ wounds. Care should be taken with clinic sanitisation, hand washing and personal protection equipment, wound care procedures and disposal of contaminated dressing materials.

Clinicians must be able to confidently distinguish the signs and symptoms of:

- Each stage of wound healing
- Excessive inflammation caused by underlying comorbidities
- Increasing bacterial burden
- Infection[28,29].

Wounds exhibiting signs of increased bacterial burden, wounds in locations at risk of persistent bacterial contamination (close to mucosal orifices, e.g. anus) and wounds in immunocompromised patients should be considered for antimicrobial dressings[29]. Wounds that have progressed to localised wound infection or spreading deep infection should be dressed with a topical antimicrobial dressing in conjunction with an appropriate systemic antibiotic medication [25,28,29]. In addition, palliative wounds may require the highly specific use of the antibiotic metronidazole to assist in control of malodour in fungating wounds. This treatment should be initiated by specialist wound care practitioners. When a wound becomes infected a wound swab should be obtained using the Levine technique, for microbiological culture and antibiotic sensitivities. This will assist in the selection of an appropriate systemic antibiotic medication [25,28,29].

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Topical antiseptics are recommended as they have a broad spectrum of antimicrobial activity and antimicrobial resistance is rare in human pathogens. In addition modern preparations have low toxicity to human cells[28,31]. Choice of antiseptic is influenced by:

- Clinician’s familiarity with the product
- Availability and cost implications
- Ease of use and implications from availability
- Wound care
- Efficacy and safety[29].

Non-cytotoxic wound irrigation solutions should be considered for wounds at risk of infection or already infected, such as PHMB with surfactant, hypochlorous acid and octenidine[27,29]. Use of cytotoxic irrigation solutions such as povidone-iodine should be limited.

Impregnated dressing materials are another form of antiseptic that can be used, and include silver (ionic salts and compounds), iodine (povidone and cadexomer), PHMB, medical grade honey, oxidase enzymes, and hydrophobic fatty acids[27,29]. Antiseptic dressing products should be applied to the cleansed wound bed according to the manufacturer’s instructions. Dressings should be changed according to the manufacturer’s instructions or at the first sign of wound fluid leakage or dressing strike-through[32].

The ‘2 week’ challenge rule should apply to determine the duration of use of an antiseptic dressing[30]. Failure of the wound to improve after this time is an indicator to change antiseptic agent and / or add an appropriate systemic antibiotic if signs of infection are progressing[31]. The incorporation of a method of aggressive wound debridement will assist to control bacterial biofilms and wound healing[28,31,33]. An antiseptic dressing should be ceased immediately at the development of signs of an adverse event such as periwound sensitisation or allergic reactions[28].

Other measures to reduce bacterial burden without the risk of antibiotic resistance have been suggested and include[32].

- Sequestration: The ability of a dressing to absorb and retain bacteria in the dressing material. This is a property of alginate, hydrofibre and hydrophobic dressings
- Larval therapy (Lucilia sericata fly maggots): This demonstrates bactericidal effects on many wound pathogens and bacterial biofilms
- Hyperbaric oxygen therapy: This increases the killing ability of the patient’s leucocytes, eliminates anaerobic bacteria and inhibits toxin formation by anaerobic bacteria
- Topical negative wound therapy: This promotes the formation of granulation tissue to improve the exposure of wound pathogens to host defence mechanisms, decreases the presence of fibrinous slough, a harbour for bacteria, and through removal of exudate decreases planktonic bacteria in the wound.
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8 Use risk assessment and management
Assessing the potential risks of infection is very important, it is only when you are able to identify the risks that you are able to develop measures to prevent infection. Risk factors for wound infection include intrinsic factors such as diseases-altering immune status (diabetes mellitus) and vascularity, and extrinsic factors such as smoking and nutrition. Obtaining a thorough history should identify risk factors for infection, and modifications that may be required for prescribing. The risks to a patient also need to be understood and taken into account before the decision is taken to prescribe.3,35

Managing risk must be a global response to the issue of antibiotic resistance; it is only when this issue and its prevention is approached by all nations together do we have a chance of reversing the present trend towards a time of no antibiotics. Much research needs to be conducted and funds provided for alternate ways of preventing infection such as new vaccines. There is an urgent need for agreement on regulating and controlling the appropriate use of antibiotics worldwide.35,36

9 Employ wound cleansing
Wound cleansing has many objectives, including preparation for a wound culture, improved assessment of the wound bed, and removal of devitalised tissue, dressing product, excess exudate and debris. In general an innocuous solution such as normal saline or potable tap water is sufficient as long as used in appropriate quantities.

Where a wound is heavily contaminated or believed to be at very high risk of infection, an antiseptic solution may be appropriate. In order to be effective but remain safe, the solution must be at the correct dilution and remain in contact with the wound bed for a sufficient time period to allow the antimicrobial to exert its effect.37

The manufacturer’s literature should be consulted for guidance on these points. More recently the use of antiseptic cleansers has been suggested alongside maintenance debridement to reduce the occurrence or recurrence of biofilm. Under most circumstances debridement alone will reduce the bioburden, but because of the propensity of biofilm to reform, an antiseptic solution or antimicrobial dressing may prove useful.38

10 Improve population health and healthcare systems to reduce hospital admissions
One of the most important methods of reducing antibiotic use and thereby resistance is by improving the general health of the population to reduce their need for hospitalisation and exposure to multiresistant bacteria. More funds need to be spent on proactive health management rather than reactive policies, and to support prevention strategies including diet improvement, more exercise, smoking cessation and improved lifestyle. The major economies must play a vital role in ensuring that such improvements are worldwide and not restricted to the developed world.39

Conclusion
Antibiotics have been one of the most significant advances in medicine but unfortunately, owing to over-use and misuse, the development of resistance to these agents has now been identified as one of the greatest threats to human health. Education on how to improve the management of antibiotic resistance is relevant to everyone. Urgent action is required as in the foreseeable future we may not have antibiotics to treat infection.
Woundox® Irrigation Solution is a powerful, rapidly acting, broad spectrum, topical antimicrobial solution that will not allow the formation of bacterial resistance.

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