Multi-resistant Infections: A Global Concern

Associate Professor Geoff Sussman

What is antimicrobial resistance?

• Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it.
What is antimicrobial resistance?

- Resistant microorganisms (including bacteria, fungi, viruses and parasites) are able to withstand attack by antimicrobial drugs, such as antibacterial drugs (e.g., antibiotics), antifungals, antivirals, and antimalarials, so that standard treatments become ineffective and infections persist, increasing the risk of spread to others.

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.
What is the difference between antibiotic and antimicrobial resistance?

Antibiotic resistance refers specifically to the resistance to antibiotics that occurs in common bacteria that cause infections.

Antimicrobial resistance is a broader term, encompassing resistance to drugs to treat infections caused by other microbes as well, such as parasites (e.g. malaria), viruses (e.g. tuberculosis and HIV) and fungi (e.g. Candida).

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; globalization 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 spread.

Huttner et al. Antimicrobial Resistance and Infection Control 2013, 2:31

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.

Huttner et al. Antimicrobial Resistance and Infection Control 2013, 2:31
Novel antimicrobials are urgently needed; in recent decades pharmaceutical companies have largely abandoned antimicrobial discovery and development given their high costs and low yield.

Huttner et al. Antimicrobial Resistance and Infection Control 2013, 2:31

Educational programs targeting both antimicrobial prescribers and consumers must be further developed and supported. The general public must continue to be made aware of the current scale of AMR’s threat, and must perceive antimicrobials as they are: a non-renewable and endangered resource.

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Antibiotic Resistance

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 healthcare facilities around the world, bacterial pathogens that express multiple resistance mechanisms are becoming common.

Antibiotic Resistance

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 undergo physiological changes that improve resistance to biocides.

It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.
Antimicrobial resistance kills

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 infection.

AMR hampers the control of infectious diseases

- Antimicrobial resistance reduces the effectiveness of treatment; thus patients remain infectious for a longer time, increasing the risk of spreading resistant microorganisms to others. For example, the emergence of *Plasmodium alciparum* resistance in the Greater Mekong subregion is an urgent public health concern that is threatening global efforts to reduce the burden of malaria.
AMR increases the costs of health care

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.

AMR increases the costs of health care

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.
Present situation Resistance in bacteria

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 kill.

- Treatment failure to the drug of last resort for gonorrhoea – third-generation cephalosporins – has been confirmed in several countries. Untreatable gonococcal infections result in increased rates of illness and complications, such as infertility, adverse pregnancy outcomes and neonatal blindness, and has the potential to reverse the gains made in the control of this sexually transmitted infection.

- Resistance to one of the most widely used antibacterial drugs for the oral treatment of urinary tract infections caused by *E. coli* – fluoroquinolones – is very widespread.
• Resistance to first-line drugs to treat infections caused by *Staphylococcus aureus* – a common cause of severe infections acquired both in health-care facilities and in the community – is also widespread.

• Resistance to the treatment of last resort for life-threatening infections caused by common intestinal bacteria – carbapenem antibiotics – has spread to all regions of the world. Key tools to tackle antibiotic resistance – such as basic systems to track and monitor the problem – reveal considerable gaps. In many countries, they do not even seem to exist.

### Resistance in tuberculosis

In 2012, there were an estimated 450 000 new cases of MDR-TB in the world. Globally, 6% of new TB cases and 20% of previously treated TB cases are estimated to have MDR-TB, with substantial differences in the frequency of MDR-TB among countries. Extensively drug-resistant TB (XDR-TB, defined as MDR-TB plus resistance to any fluoroquinolone and any second-line injectable drug) has been identified in 92 countries, in all regions of the world.
In 2011 an international network, named the World Alliance Against Antibiotic resistance (WAAR). It gathers health professionals, veterinarians, environment specialists, economists, politicians and delegates of the public. This association is supported by 51 professional societies and counts 470 members, from 45 different countries.

Bacteria do not live in isolation, but are readily dispersed through the world by humans, animals, plants, soil, water, and air. An underappreciated exposure route for the dissemination of antibiotic resistance is water, and multidrug-resistant bacteria have been detected from various water sources, including drinking water.

Current water quality guidelines tend to focus only on specific bacteria, but do not have appropriate guidance for the presence of antibiotics introduced by manufacturers, domestic disposal, agriculture, and/or the medical sector.
Antibiotic Resistance in Gram(+)’s

- 65% nosocomial blood stream infections are Gram(+) 
- Increasing resistant Gram(+) - MRSA/E, PRSP, VRE 
- VREF hospital acquired infections increased 20x between January 1989 and March 1993 (Centers for Disease Control) 
- Mortality of VRE bacteremia is 50% 
- Reports of Intermediate glycopeptide resistance in Staphylococcus spp. (GISA, GISE, GRSE)

“We face the prospect of untreatable bacterial infections, a situation not encountered since the pre-antibiotic era with a critical need for new agents”
The CDC describes an infectious disease landscape in which 2 million people in the United States are sickened annually with antibiotic-resistant infections. The report estimates that at least 23,000 people a year die from antibiotic-resistant infections. It is emphasized that these numbers are very conservative estimates.

In addition, the report quantifies the effects of antibiotic use on the number of illnesses and deaths resulting from *Clostridium difficile* infections. The report estimates that at a minimum, 250,000 illnesses and 14,000 deaths from *C difficile* are directly related to antibiotic use and resistance.
They took the study that found the highest cost of antimicrobial resistance, of $55bn per year overall to the US, and compared it with economic burden figures for other health problems in the US. These burden figures are taken from a variety of studies, and the dates range considerably, but it is clear that resistance rates fairly low down. However, the costs of resistance could be much higher than these estimates suggest.

To calculate the true economic burden of resistance we have to consider the burden associated with not having any effective antimicrobial drugs. And, as witnessed when there are outbreaks of hospital acquired infection, the system can very quickly come to a Standstill. In the future we may need to rethink how the health system is developed if effective antibiotic treatments are no longer available.
Inappropriate use of medicines leads to drug resistance.

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.

Inappropriate use of medicines leads to drug resistance.

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

Sub-therapeutic doses of antibiotics are used in animal-rearing for promoting growth or preventing diseases. This can result in resistant microorganisms, which can spread to humans.
CHANGING RESISTANCE TO SOME PATHOGENS

Escherichia coli

amoxy/clav 10%
ampicillin 46%
cotrimoxazole 17%
trimethoprim 18%
CHANGING RESISTANCE TO SOME PATHOGENS

**Haemophilus influenzae**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ampicillin</td>
<td>21%</td>
</tr>
<tr>
<td>cotrimoxazole</td>
<td>11%</td>
</tr>
</tbody>
</table>

**Klebsiella pneumoniae**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>amoxy/clav</td>
<td>7%</td>
</tr>
<tr>
<td>cephalexin</td>
<td>13%</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>4%</td>
</tr>
<tr>
<td>cotrimoxazole</td>
<td>12%</td>
</tr>
<tr>
<td>trimethoprim</td>
<td>16%</td>
</tr>
</tbody>
</table>
CHANGING RESISTANCE TO SOME PATHOGENS

*Streptococcus pneumoniae*

cotrimoxazole 33%
macrolides 16%
penicillin 24%
tetracyclines 15.7
trimethoprim 48%

Penicillin resistance in 10 629 strains of *Neisseria gonorrhoeae*

<table>
<thead>
<tr>
<th>Country</th>
<th>Tested (N)</th>
<th>Resistant or less susceptible (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>3 772</td>
<td>17</td>
</tr>
<tr>
<td>China</td>
<td>1 254</td>
<td>92.5</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>3 378</td>
<td>63.3</td>
</tr>
<tr>
<td>Japan</td>
<td>200</td>
<td>77.8</td>
</tr>
<tr>
<td>Korea</td>
<td>212</td>
<td>77.8</td>
</tr>
<tr>
<td>Singapore</td>
<td>200</td>
<td>51.5</td>
</tr>
</tbody>
</table>
**Quinolone** resistance in 10,629 strains of *Neisseria gonorrhoeae*

<table>
<thead>
<tr>
<th>Country</th>
<th>Tested (N)</th>
<th>Resistant or less susceptible (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>3,772</td>
<td>14</td>
</tr>
<tr>
<td>China</td>
<td>1,254</td>
<td>93.4</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>3,378</td>
<td>88.6</td>
</tr>
<tr>
<td>Japan</td>
<td>200</td>
<td>85.5</td>
</tr>
<tr>
<td>Korea</td>
<td>212</td>
<td>96.7</td>
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<tr>
<td>Singapore</td>
<td>200</td>
<td>56</td>
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</tbody>
</table>

**Tetracycline** resistance in 10,629 strains of *Neisseria gonorrhoeae*

<table>
<thead>
<tr>
<th>Country</th>
<th>Tested (N)</th>
<th>Resistant or less susceptible (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>3,772</td>
<td>11</td>
</tr>
<tr>
<td>China</td>
<td>1,254</td>
<td>32.1</td>
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<tr>
<td>Hong Kong</td>
<td>3,378</td>
<td>not tested</td>
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<tr>
<td>Japan</td>
<td>200</td>
<td>3.8</td>
</tr>
<tr>
<td>Korea</td>
<td>212</td>
<td>1.9</td>
</tr>
<tr>
<td>Singapore</td>
<td>200</td>
<td>58.5</td>
</tr>
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</table>
Development of antibiotic resistance in Gram negative bacilli

To determine the distribution of bacterial pathogens causing nosocomial Infections and their antibiogram, a surveillance data from January to December 2011. A total of 1800 samples from different sources were included in the study like pus, blood, urine, sputum, etc., which were taken from patients admitted in the hospital for more than a week. Gram negative bacilli were isolated, identified, and subjected to antibiotic sensitivity test.

Out of the total 1800 samples included, maximum positivity was found in the pus samples (70%). Extended-spectrum beta-lactamase (ESBL) positivity was also maximum in the pus samples (90%). These ESBL positive organisms were further subjected to antibiotic sensitivity tests and huge amounts of resistance was noted to the conventional drugs including the higher end agents like Carbapenems.
Results

Table 1: Sample Distribution

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Total No.</th>
<th>Positive sample</th>
<th>Percentage positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>766</td>
<td>276</td>
<td>37</td>
</tr>
<tr>
<td>Blood</td>
<td>428</td>
<td>50</td>
<td>11</td>
</tr>
<tr>
<td>Pus</td>
<td>216</td>
<td>152</td>
<td>70</td>
</tr>
<tr>
<td>Sputum, throat swab</td>
<td>106</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>Stool</td>
<td>44</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Fluid</td>
<td>40</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Lack of New Antibiotics

In 2012, antibiotic development continues to stagnate. Two systemic antibacterial agents have been approved for use in humans by the U.S. FDA from 2008 through the current year. Compare that to sixteen that were approved from 1983-1987. In particular, we have had no new classes of antibiotics to treat Gram-negative bacilli for more than 40 years – amazingly, the fluoroquinolones were the last new class of antibiotics to treat Gram-negative bacilli. Meanwhile, antibiotic resistance continues to spread like wildfire, particularly among the Gram-negative bacilli.
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.

<table>
<thead>
<tr>
<th>Antibiotic class; example</th>
<th>Year of discovery</th>
<th>Year of introduction</th>
<th>Year resistance observed</th>
<th>Mechanism of action</th>
<th>Activity or target species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfadiazine; prodrugs</td>
<td>1912</td>
<td>1936</td>
<td>1942</td>
<td>Inhibition of dihydropteroate synthetase</td>
<td>Gram-positive bacteria</td>
</tr>
<tr>
<td>β-lactam; penicillin</td>
<td>1928</td>
<td>1938</td>
<td>1945</td>
<td>Inhibition of cell wall biosynthesis</td>
<td>Broad-spectrum activity</td>
</tr>
<tr>
<td>Aminoglycosides; streptomycin</td>
<td>1943</td>
<td>1946</td>
<td>1946</td>
<td>Binding of 30S ribosomal subunit</td>
<td>Broad-spectrum activity</td>
</tr>
<tr>
<td>Chloramphenicol, chloromycetin</td>
<td>1946</td>
<td>1948</td>
<td>1950</td>
<td>Binding of 50S ribosomal subunit</td>
<td>Broad-spectrum activity</td>
</tr>
<tr>
<td>Macrolides; erythromycin</td>
<td>1948</td>
<td>1951</td>
<td>1955</td>
<td>Binding of 50S ribosomal subunit</td>
<td>Broad-spectrum activity</td>
</tr>
<tr>
<td>Tetracyclines; chlorotetracycline</td>
<td>1944</td>
<td>1952</td>
<td>1950</td>
<td>Binding of 30S ribosomal subunit</td>
<td>Broad-spectrum activity</td>
</tr>
<tr>
<td>Rifamycins; rifampicin</td>
<td>1957</td>
<td>1958</td>
<td>1962</td>
<td>Binding of RNA polymerase β-subunit</td>
<td>Gram-positive bacteria</td>
</tr>
<tr>
<td>Glycopeptides; vancomycin</td>
<td>1953</td>
<td>1958</td>
<td>1960</td>
<td>Inhibition of cell wall biosynthesis</td>
<td>Gram-positive bacteria</td>
</tr>
<tr>
<td>Quinolones; ciprofloxacin</td>
<td>1961</td>
<td>1968</td>
<td>1968</td>
<td>Inhibition of DNA synthesis</td>
<td>Broad-spectrum activity</td>
</tr>
<tr>
<td>Streptogramins; streptogramin B</td>
<td>1963</td>
<td>1968</td>
<td>1964</td>
<td>Binding of 30S ribosomal subunit</td>
<td>Gram-positive bacteria</td>
</tr>
<tr>
<td>Oxazolidinones; linezolid</td>
<td>1955</td>
<td>2000</td>
<td>2001</td>
<td>Binding of 30S ribosomal subunit</td>
<td>Gram-positive bacteria</td>
</tr>
<tr>
<td>Lipopeptides; daptomycin</td>
<td>1986</td>
<td>2003</td>
<td>1987</td>
<td>Depolarization of cell membrane</td>
<td>Gram-positive bacteria</td>
</tr>
<tr>
<td>Fidaxomicin targeting Clostridium difficile</td>
<td>1948</td>
<td>2011</td>
<td>1977</td>
<td>Inhibition of RNA polymerase</td>
<td>Gram-positive bacteria</td>
</tr>
<tr>
<td>Erythromycin; hederinolide</td>
<td>1997</td>
<td>2012</td>
<td>2006</td>
<td>Inhibition of F1, F2, ATPase</td>
<td>Narrow-spectrum activity (Mycobacterium tuberculosis)</td>
</tr>
</tbody>
</table>
Topical Wound Management

Antibacterials may be used topically with care
They include:

- Antibiotics
- Antiseptics

Topical Antibiotics

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.

Mupiricin a specific topical antibiotic with no similar compounds used systemically or orally.
Topical Antibiotics

- Don’t penetrate tissue
- Decompose in contact with tissue
- Diluted by exudate and decomposition
- Inhibition of contraction
- Delay re-epithelialisation
- Can cause sensitization
- Induce Resistance
- Mostly formulated to be applied to skin (or elsewhere) and act locally, not for exposed tissue

The overall evidence on the efficacy of topical antimicrobials in the management of wounds is confusing. Most use is based on laboratory studies and not on clinical research.

Some of the research use animal models and there is debate as to how relevant these studies are to chronic wounds.
Topical Antiseptics

There have been many substances used topically over thousands of years, including Hypochlorites, Peroxides, Acetic Acid, Honey etc. Over the past ten years the evidence supports the used in particular of the following:

- Iodine
- Silver
- PHMB

Iodine

Iodine in its various forms has been used as a topical antiseptic since 1840. The newer forms of iodophores have been used since the 1950’s. Most of these new forms combine iodine in a complex with a polymer eg. Povidone, Cadexomer these slowly release the iodine. Iodine is active against bacteria, mycobacteria, fungi, Protozoas, spores and viruses. There is no evidence of resistance to Iodine.
What is Silver?

Silver is a metallic element that in solution, exhibits Three Forms Ag+, Ag++ and Ag+++, each capable of forming inorganic and organic compounds and chemical complexes. Compounds involving Ag++ or Ag+++ are unstable or insoluble in water. Silver ions attack multiple microbial cells sites compared with antibiotics that mostly attack only one

Silver is effective against a broad range of aerobic, anaerobic, gram-negative and gram-positive bacteria, yeast, filamentous fungi and viruses. The experience of many clinicians, and more recent systematic reviews and meta-analyses, have confirmed positive effects of silver dressings when used appropriately.
Should Silver dressings be used in children?
Silver dressings should be used in the treatment of children with caution and the dressings should not be used for more than two weeks without good clinical reasons. Silver dressings are toxic to wounds and delay healing. Silver dressings should not be used on wounds where bioburden is not a problem, i.e., they should be reserved for use in wounds with or at risk of high bioburden or local infection.

**Bacteria become resistant to silver**
An apparent lack of response to silver does not relate to resistance, rather to inappropriate treatment of the underlying infection and/or wound aetiology.

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**What do we mean by the two-week challenge?**

**THE TWO WEEK 'CHALLENGE'**
It has been recommended that antimicrobial dressings should be used for two weeks initially and then the wound, the patient, and the management approach should be re-evaluated. The consensus group has suggested that this initial two-week period can be seen as a two-week 'challenge' period during which the efficacy of the silver dressing can be assessed.
What do we mean by the two-week challenge?

If after two weeks:

- there is improvement in the wound, but continuing signs of infection it may be clinically justifiable to continue the silver dressing with further regular reviews

- the wound has improved and the signs and symptoms of wound infection are no longer present – the silver dressing should be discontinued

- there is no improvement – the silver dressing should be discontinued and consideration given to changing the dressing to one that contains a different antimicrobial agent and if the patient is unwell using a systemic antibiotic and re-evaluating possibly untreated comorbidities.

INTERNATIONAL CONSENSUS

When not to use silver dressings

- In the absence of signs of localised (overt or covert), spreading or systemic infection
- Clean surgical wounds at low risk of infection,
  - eg donor sites, closed surgical wounds
- Chronic wounds healing as expected according to comorbidities and age
- Small acute wounds at low risk of infection
- Patients who are sensitive to silver or any of the dressing components
- Wounds being treated with enzymatic debridement

INTERNATIONAL CONSENSUS
When not to use silver dressings

- During pregnancy or lactation
- When contraindicated by the manufacturer, for example, some manufacturers recommend that their silver dressings are not used during magnetic resonance imaging (MRI), or on/near body sites undergoing radiotherapy

Silver dressings should be used in the context of accepted standard wound care which involves a holistic assessment of the patient and the wound, management of underlying comorbidities, and wound bed preparation

INTERNATIONAL CONSENSUS

The major roles for antimicrobial dressings such as silver dressings in the management of wounds are to:

- reduce bioburden in acute or chronic wounds that are infected or are being prevented from healing by microorganisms
- act as an antimicrobial barrier for acute or chronic wounds at high risk of infection or re-infection
PHMB

Polyhexanide a Biguanid antiseptic related to Chlorhexidine. PHMB was recognised as possessing superior antimicrobial effect to other cationic biocides. PHMB is marketed as a broad-spectrum antimicrobial agent in a number of diverse applications. PHMB was shown to bind rapidly to the envelope of both Gram-positive and Gram-negative bacteria. The toxicity profile of polymeric biguanides is excellent; it is not a primary skin irritant nor a hypersensitising agent.

Recommendations

Figure 1: When to implement antimicrobial dressings (adapted from [16]).

- Contamination
- Colonisation
- Localised Infection
- Spreading Infection
- Systemic Infection

Topical antimicrobial dressings are not indicated because bioburden is not causing clinical problems.

Topical antimicrobial dressings indicated.

Systemic antibiotics + topical antimicrobial dressings indicated.

*Including critical colonization (also known as covert or 'silent' infection or 'pre-infection'). Patients with chronic wounds often have commensalities that suppress the signs of inflammation and make identification of infection difficult.

NB: Treatment for wound infection should take place in the context of standard care for the wound type, e.g. debridement, offloading and correction of underlying factors such as ischaemia and hypoglycaemia to enhance the patient’s healing potential and ability to fight infection.
Prudent Use to ↓ Resistance

- Use antibiotics only when necessary
- Select agent with narrow spectrum
- Reserve broad spectrum agents for more resistant bacteria
- Continue for an “appropriate” duration
- Avoid chronic prophylaxis if possible
- Policy (guidelines, formulary, restrictions)
- Monitor trends in microbial sensitivity
- Pharmacokinetic/Pharmacodynamic Optimisation
- Cycling of antibiotics

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**Box 1. Measures to counter the threat of antibiotic resistance**

- Limit antibiotic use in general.
- Increase public awareness of the antibiotic resistance problem. Several campaigns can be considered good practice: Australia – Antibiotic Awareness Week; Canada – AntibioticAwareness.ca; Europe – Antimicrobial Resistance; United States – Get Smart: Know When Antibiotics Work. In India, clinicians are calling for a national policy to ban the sale of antibiotics over the counter, a practice currently leading to the excessive use of antibiotics [7].
- Put basic research on a broad basis.
- Increase cooperation between industry and academia.
- Accelerate the antibiotic development process and facilitate clinical studies.
- Lower too high regulatory hurdles.
- Distribute the burden of financing onto different players.
- Create long-lasting financing mechanisms.
The Future of Antibiotics and Resistance

In its recent annual report on global risks, the World Economic Forum concluded that “arguably the greatest risk . . . to human health comes in the form of antibiotic-resistant bacteria. We live in a bacterial world where we will never be able to stay ahead of the mutation curve.

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The Future of Antibiotics and Resistance

World Economic Forum report underscores the facts that antibiotic resistance and the collapse of the antibiotic research and development pipeline continue to worsen despite our ongoing efforts on all these fronts.

n engl j med 368;4 nejm.300 org january 24, 2013
Preventing infection and resistance

“Self-cleaning” hospital rooms; automated disinfectant application through misting, vapor, radiation, etc.

Novel drug-delivery systems to replace IV catheters; regenerative-tissue technology to replace prosthetics; superior, noninvasive ventilation strategies

Improvement of population health and health care systems to reduce admissions to hospitals and skilled nursing facilities

Niche vaccines to prevent resistant bacterial infections

Refilling antibiotic pipeline by aligning economic and regulatory approaches

Government or nonprofit grants and contracts to defray up-front R&D costs and establish nonprofits to develop Antibiotics

Institution of novel approval pathways (e.g., Limited Population Antibiotic Drug proposal)
New Interventions to Address the Antibiotic-Resistance Crisis.*

**Preserving available antibiotics, slowing resistance**

Public reporting of antibiotic-use data as a basis for benchmarking and reimbursement

Development of and reimbursement for rapid diagnostic and biomarker tests to enable appropriate use of Antibiotics

Elimination of use of antibiotics to promote livestock growth

New waste-treatment strategies; targeted chemical or biologic degradation of antibiotics in waste

Studies to define shortest effective courses of antibiotics for infections

n engl j med 368;4 nejm.300 org january 24, 2013

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New Interventions to Address the Antibiotic-Resistance Crisis.*

**Developing microbe-attacking treatments with Diminished potential to drive resistance**

Immune-based therapies, such as infusion of monoclonal antibodies and white cells that kill microbes

Antibiotics or biologic agents that don’t kill bacteria but alter their ability to trigger inflammation or cause disease

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### New Interventions to Address the Antibiotic-Resistance Crisis.*

**Developing treatments attacking host targets rather than Microbial targets to avoid selective pressure driving Resistance**

- Direct moderation of host inflammation in response to infection (e.g., cytokine agonists or antagonists, PAMP receptor agonists)
- Sequestration of host nutrients to prevent microbial access to nutrients
- Probiotics that compete with microbial growth

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### Conclusions:

The situation is quite dangerous. The time is not far when we will be back in the dark ages of the preantibiotic era. The need of the hour is to be alert of the gravity of this situation and take necessary measures to halt its progress.

Conclusion

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 how long to use them.