ABSTRACT
Antimicrobial resistance (AMR) increases the morbidity, mortality, and costs of treating infectious diseases. (Hawkey and Jones, 2009). The threat from resistant organisms is now a global problem, both in the hospital and to some extent in the community. The key drivers are: medical care complexity; widespread antimicrobial use in animal husbandry; antimicrobial contaminated food distribution; international travel, and food distribution of food contaminated with multidrug resistant organism. Strategies for infection control are: good understanding of what needs to be done, consistent application of infection control measures, use of "search and destroy" techniques; and effective antimicrobial stewardship. This paper reviews the current issues and potential solutions.

Keywords: multidrug resistant organisms, infectious disease

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ANTIMICROBIAL RESISTANCE

Illustrative cases
Three cases are used to illustrate the pervasiveness of multidrug resistant organisms in present day Singapore.

CASE 1 – Multidrug resistant E coli
An elderly Chinese female with no travel history, who was deskbound and watched her stocks and shares on a laptop was admitted for urinary tract infection. She was found to have a multidrug resistant E coli Infection. The profile of the causative organism was:
- Resistant to ampicillin, augmentin, ceftriaxone, cefepime, gentamicin, amikacin, ciprofloxacin, Bactrim, doxycycline, piperacillin/ tazobactam.
- Resistant to ertapenem.
- Sensitive to imiprenem/ meropenem.

CT abdomen showed bilateral pyelonephritis. She stayed many weeks in hospital for her multidrug resistant E coli infection to be brought under control.

CASE 2 – Multidrug resistant Klebsiella pneumoniae
An elderly Malay man with no travel history is seen for benign enlarged prostate. He is found to have an urinary tract infection. Isolates from the urine culture and sensitivity showed multidrug resistant Klebsiella pneumoniae. He was ill and had to be admitted to ICU. The profile of the causative organism was:
- Resistant to ampicillin augmentin, ceftriaxone, cefepime, gentamicin, amikacin, ciprofloxacin, Bactrim, doxycycline, piperacillin/ tazobactam, impenem, cropenam.
- Resistant to polymyxin B.
- Intermediate resistance to aztrenam.

CASE 3 - Several multidrug resistant organisms
An elderly Singapore female patient went to Mumbai for holiday. She was knocked down by a bus and sustained an open wound. She was admitted to a Mumbai hospital for a day and subsequently flew back to Singapore for treatment. She was found to have several organisms isolated from her wound that were resistant to carbapenem as shown in Table 1. Blood culture was positive for multidrug resistant Klebsiella pneumoniae. She stayed many months in hospital before she was fit for discharge.

TABLE 1. ISOLATES FROM PATIENT ADMITTED TO MUMBAI HOSPITAL

<table>
<thead>
<tr>
<th>Organism</th>
<th>Site</th>
<th>Carbapenem</th>
<th>Resistance Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Wound</td>
<td>Resistant</td>
<td>NDM-1</td>
</tr>
<tr>
<td>Pseudomonas putida</td>
<td>Wound</td>
<td>Resistant</td>
<td>NDM-1</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>Wound</td>
<td>Resistant</td>
<td>NDM-1</td>
</tr>
<tr>
<td>Citrobacter sediakii</td>
<td>Wound</td>
<td>Resistant</td>
<td>NDM-1</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>Wound</td>
<td>Resistant</td>
<td>Other</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>Wound</td>
<td>Resistant</td>
<td>OXA-23</td>
</tr>
<tr>
<td>Klebsiella pneumonia</td>
<td>Blood</td>
<td>Resistant</td>
<td>NDM-1</td>
</tr>
</tbody>
</table>

Footnotes
NDM-1 stands for New Delhi metallo-beta-lactamase, an enzyme produced by bacteria like E.coli and Klebsiella pneumonia that confers antibiotic resistance to all common penicillins, cephalosporins and the carbapenems. The only drug that has been shown to be reasonably effective is colistin, an antibiotic that has not been used in the past few decades because of its toxicity. Essentially, we do not have the capability to treat our patients with effective antibiotics if they were to have this infection.

Multidrug resistant organisms (MDROs)
Table 1 shows the major antibiotic resistant bacteria contributing to the burden of resistance.
TABLE 2. MAJOR ANTIBIOTIC-RESISTANT BACTERIA CONTRIBUTING TO THE BURDEN OF RESISTANCE

<table>
<thead>
<tr>
<th>Gram-positive bacteria</th>
<th>Gram-negative bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Enterococcus species</td>
<td>Acinetobacter baumannii</td>
</tr>
<tr>
<td>Escherichia coli and</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td></td>
</tr>
<tr>
<td>resistant to third-</td>
<td></td>
</tr>
<tr>
<td>generation cephalosporins</td>
<td></td>
</tr>
</tbody>
</table>

**Resistance in Gram positive bacteria**

Methicillin resistant Staph aureus is widely distributed globally and increasing with levels of MRSA reaching 30% in many countries. There is now the emergence of community-associated MRSA (CA-MRSA) which are genetically unrelated to the hospital acquired strains of MRSA. Cases of CA-MRSA usually present in younger patients without underlying risk factors, and typically cause skin and soft tissue infections (SSTIs). (Hawkey, Jones, 2009). The emergence of metallo-beta-lactamases with activity against carbapenems with activity against carbapenems has now occurred and compromised the clinical utility of this class of antibiotics. Rising fluoroquinolone resistance is also present in Europe. (Hawkey, Jones, 2009). The spread of ESBL-producing organisms within institutions can be slowed by the use of barrier protection and restriction of later generation cephalosporins. (Munroz-Price, 2014). The emergence of metallo-beta-lactamases with activity against carbapenems has now occurred and compromised the clinical utility of this class of antibiotics. Rising fluoroquinolone resistance is also present in Europe. (Hawkey, Jones, 2009). The spread of ESBL-producing organisms within institutions can be slowed by the use of barrier protection and restriction of later generation cephalosporins. (Munroz-Price, 2014). Fortunately, most ESBLs do not break down cephamycins or carbapenems and are susceptible to beta-lactamase inhibitors.

The best therapeutic option for severe infections caused by ESBL-producing organisms is a carbapenem (imipenem, meropenem, doripenem, andertapenem). Cefepime may be effective against ESBL-producing organisms that test susceptible if administered in high doses (ie, 2 g every eight hours). Use of other cephalosporins and piperacillin-tazobactam has been associated with treatment failures. (Munroz-Price, 2014). The emergence of metallo-beta-lactamases with activity against carbapenems has now occurred and compromised the clinical utility of this class of antibiotics. Rising fluoroquinolone resistance is also present in Europe. (Hawkey, Jones, 2009). The spread of ESBL-producing organisms within institutions can be slowed by the use of barrier protection and restriction of later generation cephalosporins. (Munroz-Price, 2014). Fortunately, most ESBLs do not break down cephamycins or carbapenems and are susceptible to beta-lactamase inhibitors.

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Community acquired MRSA (CA-MRSA)

What are the criteria for distinguishing community-associated MRSA (CA-MRSA) from healthcare-associated MRSA (HA-MRSA)? Persons with MRSA infections that meet all the following criteria likely to have CA-MRSA infections (CDC, 2007):
• Diagnosis of MRSA was made in the outpatient setting or by a culture positive MRSA within 48 hours after admission to hospital.
• No medical history of MRSA infection or colonisation.
• No medical history in the past year of hospitalisation; admission to a nursing home; skilled nursing facility, or hospice; dialysis; surgery.
• No permanent indwelling catheters or medical devices that pass through the skin into the body.

**DRIVERS IN THE DEVELOPMENT OF ANTIBIOTIC RESISTANCE**
Several drivers acting in concert result in the development of antibiotic resistance. The interrelationships are shown in Figure 2.
(a) Medical care complexity.
(b) Antimicrobial use in farming and animal husbandry.
(c) Microbe contaminated food distribution, and
(d) Resistant organisms dissemination through international travel.

**Medical care complexity as a driver**
Medical care complexity is contributed by the older population, more chronic diseases, inter-connected healthcare system allowing acquisition in high risk settings, as well as antibiotic-resistant bacteria laden food. The risk of bacteria acquiring drug resistance are highest in intensive care unit; moderate risk in prolonged hospitalisation, major surgery (not requiring ICU care), transfer to metropolitan tertiary hospital; and low to negligible risk in outpatient clinic visit, community hospital short stays, and community residence.

**Spiralling drug resistance.** In high risk healthcare settings, the vicious cycle of demand for stronger and stronger antibiotics is kept going by the following spiralling factors:
• A new broad spectrum antibiotic is required because of rising trends of antimicrobial resistance trends to existing antibiotics.
• There is continuing pressure for empirical therapy of the new broad spectrum antibiotic to save lives.
• More of the broad spectrum antibiotic is then prescribed resulting in greater antibiotic selection pressure.
• Higher resistance rates then occur, and
• The need for a new broad spectrum antibiotic is now created and the vicious cycle goes on.

**The arms race.** There is a need to develop effective antibiotics in healthcare fast enough to beat growing antimicrobial resistance. The phenomenon can be compared to an arms race against multidrug-resistant organisms. Winning the fight against infectious bacteria requires staying ahead of the organisms’ uncanny ability to flank our frontal assaults (Karyn Hede, 2014)10. This has been called the Red Queen phenomenon or the Red Queen’s race taken from the story of Alice in Wonderland’s encounter with the Red Queen and what she said. Table 3 shows the results of this infectious arms race since the days of penicillin.

**FIGURE 1: CA-MRSA SKIN/SOFT TISSUE INFECTIONS (SSTI) IN SINGAPORE**

FIGURE 2. SETTINGS CONTRIBUTING TO THE POOL OF ANTIMICROBIAL RESISTANCE

Source: Seiffert et al 2013

Footnote. The up arrows show the use or presence of antibiotics in each specific setting of hospital, nursing homes, and long term care facilities; as well as in the raising of food producing animals. The continuous arrows connecting the human settings (circles) and animal settings (squares) show the spread of organism between human and animal settings.

TABLE 3. AN INFECTIOUS ARMS RACE

As new antibiotics come on the market, resistance develops, but the drugs continue to be used. The growing collection of antibiotics over time is offset by the increasing resistance. Winning the fight against infectious bacteria requires staying ahead of the organisms’ uncanny ability to flank our frontal assaults.

<table>
<thead>
<tr>
<th>Antibiotic introduced</th>
<th>Antibiotic resistance appearing</th>
<th>Observations and actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin – 1943</td>
<td>Staphylococcus resistance developed before penicillin was approved 1940 – Antibiotic resistance to penicillin was discovered before the drug went on the market 1945 – Alexander Fleming warns about the misuse of antibiotics</td>
<td></td>
</tr>
<tr>
<td>Tetracycline – 1950</td>
<td>Shigella resistance 9 years later</td>
<td></td>
</tr>
<tr>
<td>Erythromycin – 1953</td>
<td>Staphylococcus resistance 15 years later</td>
<td></td>
</tr>
<tr>
<td>Methicillin – 1960</td>
<td>Staphylococcus resistance 2 years later</td>
<td></td>
</tr>
<tr>
<td>Gentamycin – 1967</td>
<td>Enterococcus resistance 12.5 years later</td>
<td></td>
</tr>
<tr>
<td>Vancomycin – 1972</td>
<td>Enterococcus resistance 16 years later</td>
<td></td>
</tr>
<tr>
<td>Cefazidime – 1985</td>
<td>Enterobacteriaceae resistance 2.5 years later</td>
<td></td>
</tr>
<tr>
<td>Imipenem – 1985</td>
<td>Enterobacteriaceae resistance 11.5 years later</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin – 1996</td>
<td>Pneumococcus resistance 0.5 year later (Quick onset of resistance)</td>
<td></td>
</tr>
<tr>
<td>Linezolid – 2000</td>
<td>Staphylococcus resistance 1.5 years later (Quick onset of resistance)</td>
<td></td>
</tr>
<tr>
<td>Daptomycin – 2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftaroline – 2010</td>
<td>Staphylococcus resistance 1.5 years later (Quick onset of resistance)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Hede, 2014 (adapted)
The empty pipeline. To add to the woes of antibiotic resistance is the paucity of new antibiotic development efforts by pharmaceutical firms is a serious challenge. A world economic forum in 2013 lamented that no new classes of antibiotics have been discovered since 1987 (WEF, 2013).

(b) Antimicrobial use in farming and animal husbandry
The need to stop using antibiotics on farm animals to promote growth is now clearly recognised and world action is taking place (See Table 3). Essentially, antibiotics should only be used to treat infections.

(c) Microbe contaminated food distribution
Distribution of contaminated food is another driver of resistant organisms. Surveillance is all important. Thus, Our Agriculture and Food service in Singapore routinely checks for common and emerging food-borne pathogens such as Salmonella, Shigella, Vibrio, Yersinia, Clostridium, Campylobacter, Listeria, Escherichia coli O157:H7 and Vancomycin Resistant Enterococci, to minimise the transmission of antimicrobial resistance and the development of illness when food is consumed. (Agri, Food, and Veterinary Authority of Singapore, 2014)

(d) Resistant organisms dissemination through international travel
This is another driver. A study of 226 travellers by Peirano et al (Peirano et al, 2011) in Canada confirmed the findings of 2 earlier Swedish studies that foreign travel, especially to the Indian subcontinent and Africa were major risks for rectal colonization with CTX-M-producing E coli through contaminated food intake and these events were most likely to contribute to the worldwide spread of these bacteria (Peirano et al, 2011). CTX-M producing E coli are bacteria that acquired beta-lactamase enzymes not by mutation but by plasmid acquisition of beta-lactamase genes from environmental bacteria (Munroz-Price, 2014). Overall, Periano et al found that 24/52 (46%) of travellers with diarrhoea returning to Canada from travel to India, Africa, or Asia were colonized with ESBL-producing organisms. (Peirano et al, 2011).

INFECTION CONTROL

Principles of infection control
Infection control begins with asking the questions in Tables 4, 5 and 6. These principles have been embodied in the Ministry of Health’s MDRO Infection Control Guidelines, 2013.
TABLE 5. WHAT IS BLOCKING PROGRESS?

- Complex problem requiring a comprehensive response among and between Member States across different sectors
- Actions needed are clear – but there is a failure of commitment, implementation and accountability
- Preventing AMR is a “public good” which strengthens health security – but financing is insufficien


TABLE 6. KEY TIERED RECOMMENDATIONS FROM THE HEALTHCARE INFECTION CONTROL PRACTICES ADVISORY COMMITTEE TO CONTAIN MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA

<table>
<thead>
<tr>
<th>Tier 1 recommendation</th>
<th>Example</th>
<th>Examples of Tier 2 recommendation</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative control and adherence monitoring</td>
<td>Obtain and document administration support</td>
<td>Obtain expert consultation</td>
<td>Use of real-time feedback to enhance adherence</td>
</tr>
<tr>
<td>Education</td>
<td>Focus on best prevention and practices for HCWs</td>
<td>Intensified educational program</td>
<td>Increase frequency of education and provide timely feedback</td>
</tr>
<tr>
<td>Antibiotic control program</td>
<td>Monitor susceptibility patterns</td>
<td>Target key antibiotic restrictions</td>
<td>Increase frequency of feedback susceptibility to clinicians</td>
</tr>
<tr>
<td>Surveillance for MDR-GNB</td>
<td>Estimate MDR-GNB burden stratified by units at risk</td>
<td>Implement Active surveillance culture</td>
<td>Active surveillance culture and track patients with MDR-GNB (e.g. use of line listing)</td>
</tr>
<tr>
<td>Infection control (e.g., contact isolation and hand hygiene)</td>
<td>Monitor adherence to basic infection control measures</td>
<td>Intensified program with monitoring and feedback</td>
<td>Use of cohort section together with real-time feedback</td>
</tr>
<tr>
<td>Environmental measure</td>
<td>Implement policy and monitor cleaning practice</td>
<td>Monitor cleaning performance using checklist or special approaches</td>
<td>(e.g. environmental cleaning) Use of nontouch technology (e.g. ultraviolet light, hydrogen peroxide vapour)</td>
</tr>
</tbody>
</table>

Source: Apisarnthanarak A et al (2013)

Search & Destroy strategies

Search & Destroy strategies have been introduced in the hospitals and also in the community. The practices in Hospitals in the Eureigo MRSA elimination initiative which is a collaboration between Holland and Germany across a section of the Dutch German border. The initiative consists of isolation and screening of high risk patient groups; screening of low risk groups; strict isolation of carriers; decolonisation of carriers (Friedrich et al, 2008). Similarly there is a search and destroy initiative in the community conducted by Bartels et al (Bartels, 2010). The authors were able to eliminate the MRSA carrier state in persons in 8 households.

ANTIBIOTIC STEWARDSHIP

There is a need for an antibiotic stewardship programme to conserve existing antibiotics. The activities have been described by Dellit et al. (Dellit, 2007). These are:

- Prospective audit and feedback.
- Antibiotic restriction through (a) permission required for prescription, and (b) antibiotic cycling.
- Other elements (a) education of providers, (b) guidelines, and (c) computerised clinical decision support.

CONCLUSIONS

- Antimicrobial resistance (AMR) is now a global problem, both in the hospital and in the community.
- Key drivers of AMR need to be addressed.

REFERENCES

LEARNING POINTS

• Antimicrobial resistance (AMR) is now a global problem, both in the hospital and to some extent in the community too.

• The key drivers for this development are medical care complexity; widespread antimicrobial use in farming and animal husbandry; contaminated food distribution; and resistant organisms dissemination through international travel.

• Strategies for infection control are: good understanding of what needs to be done; consistent application of infection control measures; use of “search and destroy” techniques; and effective antimicrobial stewardship.