Antimicrobial Resistance and Prescribing

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Year 5, Medicine

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Tw @mdj kf  http://idmic.net
Watching antibiotic resistance evolve...

https://www.youtube.com/watch?v=yybsSqcB7mE
What is Antimicrobial Resistance (AMR)?

Medicines for treating infections lose effect because the microbes change;
1. mutate
2. acquire genetic information from other microbes to develop resistance

Types of AMR

1. Antibacterial resistance (e.g. to antibiotics and other antibacterial drugs)
2. Antiviral resistance (e.g. to anti-HIV medicines)
3. Antiparasitic resistance (e.g. to anti-malaria medicines)
4. Antifungal resistance (e.g. to medicines used to treat Candidiasis)

AMR is a natural phenomenon accelerated by use of antimicrobial medicines. Resistant strains survive and aggregate.
The Future of Antibiotics and Resistance
Brad Spellberg, M.D., John G. Bartlett, M.D., and David N. Gilbert, M.D.

In its recent annual report on global risks, the World Economic Forum (WEF) 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 curve. A test of how far behind we follow ourselves to find the path to control, antibiotic, and new antibiotic research are cornerstones of society’s approach to combating resistance and must be continued. But the WEF report underscores the facts that antibiotic resistance and the collapse of the antibiotic research-karyotes (bacteria) “invented” antibiotics billions of years ago, and resistance is primarily the result of bacterial adaptation to eons of antibiotic exposure. What are the fundamental implications of this in addition to the power, their preexistences. Rather than resistance, it is not antibiotic use which resistance is driven by micro-

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January 2017: National AMR multi-sector symposium took place

Recommendations drafted against the WHO policy package on AMR under these headings:

1. National coordination mechanisms (governance)
2. Access to, and quality of, essential medicines
3. Surveillance and laboratory capacity
4. Rational use of medicines in humans and animals
5. Infection prevention and control
6. Research and development
Country Situation Analysis

• “In general, the analysis revealed that the current level of activities addressing AMR in PNG across these six elements is low.

• The most significant challenge relates to rational use of medicines in humans and animals. This challenge is driven by patients and providers alike. Patients typically self-prescribed before seeking care services, and providers over-prescribe at the point of care.

• Similarly, there is no regulation to restrict the use of critically important medicines for human use in animals, and there is no regulation to restrict the use of antimicrobials as growth promoters.”
1. Antimicrobial resistance kills

Antimicrobial resistant infections often fail to respond to standard treatment, resulting in **prolonged illness, higher health care expenditures, and a greater risk of death.**
14 yr old girl, PMGH Feb 2013

- Presented with sepsis, acute onset
- Febrile, hypotensive, thin
- Suspected endocarditis but no direct evidence
  - Given gentamicin and flucloxacillin
  - Poor response to treatment

Day 4 - Blood cultures: Gram positive cocci (staph)- identified as MRSA (methicillin-resistant Staphylococcus aureus)
PMGH stats- *Staphylococcus aureus* from blood

- 2011-12 60% of 41 events due to MRSA

- Empiric cover required

[MRSA is resistant to all available betalactam (penicillin-type) antibiotics]
Between April 1998 and March 2000, multi-resistant enteric gram-negative sepsis occurred in 106 of 5331 paediatric admissions (2%), but caused 87 (25%) of 353 deaths.
Risk of Death is Higher in Patients Infected with Resistant Strains

<table>
<thead>
<tr>
<th>Outcome (number of studies included)</th>
<th>Resistant</th>
<th>Not resistant</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Escherichia coli</strong> resistant to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd gen. cephalosporins</td>
<td>Bacterium attributable mortality (n=4)</td>
<td>23.6</td>
<td>12.6</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Bacterium attributable mortality (n=1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong> resistant to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd gen. cephalosporins</td>
<td>Bacterium attributable mortality (n=4)</td>
<td>20</td>
<td>10.1</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Bacterium attributable mortality (n=1)</td>
<td>27</td>
<td>13.6</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong> resistant to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methicillin (MRSA)</td>
<td>Bacterium attributable mortality (n=46)</td>
<td>26.3</td>
<td>16.9</td>
</tr>
</tbody>
</table>
Resistant organisms - Up to twice the risk of dying
2. AMR hampers the control of infectious diseases

AMR reduces the effectiveness of treatment; thus *patients remain infectious for a longer time, increasing the risk of spreading* resistant microorganisms to others.
Catherina Abraham

Aged 20 years, flew to Cairns from Torres Strait, 2012 diagnosed with XDR-TB.

After almost a year in an isolation ward at Cairns Base Hospital, she died on 8 March 2013.

Secondary case, aged 32 also died.

3. AMR increases the costs of health care

Resistant infections require more expensive therapies and longer duration of treatment

*Catherina’s treatment cost Queensland Health about $500 000 and would have cost $1 million had she lived to complete it.*
4. The achievements of modern medicine are put at risk by AMR

- organ transplantation
- cancer chemotherapy
- major surgery
5. AMR threatens health security, damages trade and economies

- **Thailand**
  - Population: 70m
  - >38,000 deaths
  - >3.2m hospital days
  - Overall societal costs
    - US$ 84.6–202.8 mill. direct
    - >US$1.3 billion indirect
  - Source: Pumart et al 2012

- **United States**
  - Population: 300m
  - >23,000 deaths
  - >2.0m illnesses
  - Overall societal costs
    - Up to $20 billion direct
    - Up to $35 billion indirect
  - Source: US CDC 2013

*WHO 2014*
Why is antimicrobial resistance important?

1. **Antimicrobial resistance kills**- mortality higher for resistant pathogens
2. **AMR hampers the control of infectious diseases** – prolonged infectivity – eg. Mdr-TB
3. **AMR increases the costs of health care**
4. **Achievements of modern medicine are put at risk by AMR**- eg. Leukaemia treatment
5. **AMR threatens health security, damages trade and economies**
AMR in PNG

1. WHY is it an important problem?
2. HOW has the problem arisen?
3. WHAT do we have to do?
Bacterial perspective

- 3.5 billion years of evolutionary diversification
- Estimated $10^{21}$ bacteria; one billion progeny/day
- Adapted to innumerable niches
- Sense their environment, exhibit cooperative behaviours and adaptive stress responses
- Antibiotic resistance genes are ancient
- Humans carry 2-3 kg of bacterial biomass acquired from diverse sources
How does resistance arise?

1. **mutational change** in bacterial chromosome with clonal expansion of a resistant subpopulation

   AND/OR

2. **horizontal transfer** of new resistance gene(s) from another bacterial species by direct transfer and recombination

   *Antibiotic exposure increases the rate of both processes*

   *Antibiotics select and promote growth of resistant subpopulations*
DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW

Key:
- **β-LACTAMS**: Commonly act as bacteriostatic agents, restricting growth & reproduction.
- **AMINOLYCOSEIDES**: Commonly act as bactericidal agents, causing bacterial cell death.
- **CHLORAMPHENICOL**: Commonly used in low income countries.
- **GLYCOPEPTIDES**: Common drugs of last resort.
- **QUINOLONES**: Resistance evolves rapidly.
- **OXAZOLIDINONES**: Potent antibiotics commonly used as "drugs of last resort".

**β-LACTAMS**
- Most widely used antibiotics in the NHS.
- **MODE OF ACTION**: Inhibit synthesis of proteins by bacteria, leading to cell death.
- **EXAMPLES**: Penicillin (shown) such as amoxicillin and flucloxacillin, Cephalosporins such as ceftaxime.

**AMINOLYCOSEIDES**
- Family of over 20 antibiotics.
- **MODE OF ACTION**: Inhibit synthesis of proteins by bacteria, leading to cell death.
- **EXAMPLES**: Streptomycin (shown), neomycin, kanamycin, gentamycin.

**CHLORAMPHENICOL**
- Distinct individual compound.
- **MODE OF ACTION**: Inhibit synthesis of proteins by bacteria, leading to cell death.
- **EXAMPLES**: Chloramphenicol.

**GLYCOPEPTIDES**
- Consist of carbohydrate linked to a peptide formed of amino acids.
- **MODE OF ACTION**: Inhibit synthesis of proteins by bacteria, leading to cell death.
- **EXAMPLES**: Vancomycin (shown), teicoplanin.

**QUINOLONES**
- Resistance evolves rapidly.
- **MODE OF ACTION**: Interferes with bacterial DNA replication and transcription.
- **EXAMPLES**: Ciprofloxacin (shown), levofloxacin, trovafloxacin.

**OXAZOLIDINONES**
- **MODE OF ACTION**: Inhibit synthesis of proteins by bacteria, leading to cell death.
- **EXAMPLES**: Linezolid (shown), posizolid, tedizolid, cycloserine.

**SULFONAMIDES**
- First commercial antibiotics were sulfonamides.
- **MODE OF ACTION**: Do not kill bacteria but prevent their growth and multiplication. Cause allergic reactions in some patients.
- **EXAMPLES**: Prontosil, sulfamethoxazole, sulfisoxazole.

**TETRACYCLINES**
- Becoming less popular due to development of resistance.
- **MODE OF ACTION**: Inhibit synthesis of proteins by bacteria, preventing growth.
- **EXAMPLES**: Tetracycline (shown), doxycycline, minocycline, oxytetracycline.

**MACROLIDES**
- Second most prescribed antibiotics in the NHS.
- **MODE OF ACTION**: Inhibit protein synthesis by bacteria, occasionally leading to cell death.
- **EXAMPLES**: Erythromycin (shown), clarithromycin, azithromycin.

**ANSAMYCINS**
- Can also demonstrate antiviral activity.
- **MODE OF ACTION**: Inhibit the synthesis of RNA by bacteria, leading to cell death.
- **EXAMPLES**: Geodanamycin (shown), rifamycin, naphthomycin.

**STREPTOGRAMINS**
- Two groups of antibiotics that act synergistically.
- **MODE OF ACTION**: Disrupt multiple cell membrane functions, leading to cell death.
- **EXAMPLES**: Pristinamycin IA (shown), Pristinamycin IB.

**LIPOPEPTIDES**
- Instances of resistance rare.
- **MODE OF ACTION**: Disrupt multiple cell membrane functions, leading to cell death.
- **EXAMPLES**: Daptomycin (shown), surfactin.

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[http://aimed.net.au](http://aimed.net.au)
Medscape description
Cluster-randomised sampling of newly registered smear-positive pulmonary TB patients identified by public healthcare services in Madang, Morobe, Western Provinces and National Capital District.

Number of clusters in the survey set to 40 which were distributed in 27 health centres selected using a probability-proportional to size cluster sampling strategy.
Results

• 1,182 patients with sputum-smear positive pulmonary TB enrolled.
• Of them, 1,027 were newly diagnosed cases, 154 patients had previous history of TB treatment.
• 1,146 patients were detected with TB (999 new cases, 146 previously treated cases and 1 case with undocumented history).
• HIV status available for 57% of cases - 32 (5%) were HIV positive.
• Of the 57 cases with culture and DST result, 44 (77%) cases had additional resistance to isoniazid.
• Of the 44 MDR-TB cases 20 were in new and 24 were in previously treated TB cases.
Significance

• The levels of MDR-TB found in PNG are higher than those reported by neighbouring countries:
  • PNG current study (2.7% in new and 19% in previously rx TB)
  • Indonesia (1.9% in new and 12% in previously treated TB cases)
  • Australia (1.7% in new and 10% in previously treated TB cases)
  • Philippines (2.0% in new and 21% in previously treated TB cases)
  • Viet Nam (4.0% in new and 23% in previously treated TB cases).
Antibiotic usage drives resistance!
Correlation of resistance with Antimicrobial Use in Community-Acquired Infections in Europe, 1997-2000

Each dot represents a different European nation.

A very tight relationship between overall community consumption and resistance (erythromycin is a macrolide).

Declining usage: hospital antibiotic sales (kg), IMS data
E. coli from blood & CSF in the UK - a recent fall in resistance

- coincides with decreased use = decreasing selection?
- If plasmids can’t be lost, is this strain displacement?
How are antibiotics used in PNG?

- PMGH (Steven Yennie, 2012)
  - Medical ward 72% of patients receiving an anti-infective (excluding TB and ARV treatment)

- Alotau Hospital (Nick Ferguson, Nov 2012)
  - Medical ward: 60% of patients on anti-infective
  - Obstetric ward: 34%
Common survey findings

- Very prolonged courses, prolonged IV courses
- Undocumented reasons for therapy
- Treatments not in accord with Standard Treatment Guidelines
Antibiotic exposure: unintended consequences

- Increased susceptibility to colonisation and infection by antimicrobial resistant organisms
- Prolonged changes to the bowel flora (microbiota) associated with onset of type 2 diabetes, inflammatory bowel disease, obesity, lowered lung immunity ...
- Drug interactions/side effects: e.g.
  - sudden death increase in elderly patients on ACE inhibitors + trimethoprim or bactrim (hyperkalaemia)
  - Prolonged QT and sudden death increase- macrolines, fluoroquinolones
AMR in PNG

1. WHY is it an important problem?
2. HOW has the problem arisen?
3. WHAT do we do now?
The containment of antibiotic resistance needs coordination

- **Surveillance**
  - Resistance patterns
  - Antibiotic usage
  - Health care associated infections

- **Decrease the need for antibiotics**
  - Prevention of disease
  - Prevention of bacterial spread

- **Use antibiotics properly**
  - Diagnostics
  - Rational use

- **Coordinate national activities**

- **Knowledge education, information, research**

- **International collaboration**

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React.org
Vital question - how do we preserve a scarce resource?

Personal responsibility & accountability—responsible antibiotic use and infection control

Prevent over the counter access

Leadership and governance – national and local
Infection prevention & control

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**Surveillance**
- Resistance patterns
- Antibiotic usage
- Health care associated infections

**Decrease the need for antibiotics**
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**Use antibiotics properly**
- Diagnostics
- Rational use

**Coordinate national activities**
- Knowledge education, information, research

**International collaboration**

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www.react.org
Lessons learned from Semmelweis (1861)

Hand disinfection saving women’s lives in Vienna

Intervention
May 15, 1847
Left- Hand imprint immediately after abdominal examination of a patient who was colonised with MRSA – pink colonies = MRSA

Right- hand imprint after disinfection with alcohol hand rub


MRSA= methicillin-resistant *Staphylococcus aureus*
Point of care availability of Alcohol-based hand rub at PMGH, Goroka Hospital

- Rub hands BEFORE and AFTER EVERY patient contact
- Teach patients and relatives to use the rub
“Standard precautions” : the basis for protecting ALL patients & staff

Always follow these standard precautions:

1. Perform hand hygiene before and after every patient contact.
2. Use personal protective equipment when risk of body fluid exposure.
3. Use and dispose of sharps safely.
4. Perform routine environmental cleaning.
5. Clean and reprocess shared patient equipment.
6. Follow respiratory hygiene and cough etiquette.
7. Use aseptic technique.
8. Handle and dispose of waste and used linen safely.
**F-A-S-T** strategy for TB & DR-TB control

**Finding TB Patients:**
The most infectious TB patients are the ones that we don’t know about because they are not being treated. Undiagnosed TB patients can be in clinics, waiting areas, hospital emergency rooms, and wards that care for surgical or other medical problems. Asking all patients about TB symptoms, such as chronic cough, fever, and weight loss can lead to finding previously unsuspected TB cases, as can observing patients for cough in waiting rooms, registration areas, and admission holding areas.

**Actively:**
TB is usually diagnosed passively, occurring when patients’ symptoms lead them to seek help. However, symptoms, such as cough, fever, and weight loss can be present for a long time, be attributed to other conditions, or be overshadowed by other pressing issues. The **FAST** strategy incorporates specifically trained staff called “cough monitors” or “cough surveillance officers” whose job is to identify patients with chronic cough and other TB symptoms, and promptly collect sputum, which would ideally be sent for rapid molecular testing.

**Separating safely:**
MDR-TB patients should be moved to a well-ventilated area to prevent the transmission of MDR-TB to other patients.

**Treatment:**
Treatment is the final and most important step in preventing transmission of TB to others. Patients become non-infectious soon after starting effective TB treatment.
F-A-S-T strategy for TB & DR-TB control

PMGH TB isolation facility
The AMR dilemma as a ‘Tragedy of the Commons’

“A dilemma arising from the situation in which multiple individuals, acting independently and rationally consulting their own self-interest, will ultimately deplete a shared limited resource, even when it is clear that it is not in anyone’s long-term interest for this to happen.”

Wikipedia, G Hardin 1968
Antimicrobial stewardship

- Optimise treatment of patients with infection - target treatment - make sure the right patients are getting the right drug, right dose and duration
- Minimise individual and community adverse impacts of antimicrobials

*AMR is dynamic – reducing antimicrobial usage generally leads to reductions in resistance*
PNG therapeutic resources

Adult Medicine
- Adult medical standard treatment guide- 2012
- HIV Adult standard treatment guideline 2009 March. This is the current version in use in 2012.

Paediatrics
- PNG Paediatric standard treatment guides Main resource site
- WHO Integrated Management of Childhood Illness resources
- Recommendations for management of common childhood conditions 2012. Excellent evidence-based extensive review.
- International Child Health Review Collaboration
- Royal Childrens Hospital Melbourne Paediatric Handbook 8th Edition
- WHO Treatment of Children living with HIV
- Manual on paediatric HIV care and treatment for district hospitals WHO 2011

Obstetrics and Gynaecology

Surgery
- Standard Treatment book - awaited
- WHO Guidelines for Safer Surgery 2009

See also Safer surgery: resource poor countries

PNG Medical Journal
Full index to all issues with text links are available from here. The PNMJ is indexed by Medline and so the easiest way to search.

See this quick start guide to PUBMED for more instructions. It is essential for practitioners in PNG to be aware of the local literature in PNG which have been well researched in the past.

Is therapy ‘AIMED’? – a standard for prescribers

- *Antimicrobial* selection and dosage should be compliant with guideline
- *Indication* for treatment should be documented
- *Microbiology before rx*
- *Evaluate* at 48-72hrs
- *Duration* or review date explicit

[www.aimed.net.au](http://www.aimed.net.au)
Therapeutic factors promoting antibiotic resistance

1. Antibiotic selective pressure
   - Number of patients exposed (volume of use)
   - Breadth of spectrum
   - Duration of use

2. Inadequate dosing
Eliminate unnecessary use

• Patients may receive antibiotics for extended post operative prophylaxis or for ‘just in case’ situations where there is little actual evidence of infection
• These exposures put patients at great risk of acquiring resistant organisms and should be avoided

(Antibiotics do not protect patients from poor hygiene)

Rational empirical antibiotic use

• Evaluate likelihood of sepsis by presence of SIRS, other organ system dysfunction
• Withhold antibiotics if there is not a strong case and severe sepsis is absent
• Do pre-antibiotic microbiology tests
• Select empirical antibiotic(s) based on local guidelines and AMR incidence
• Document the reason for antibiotics in the patient record
Post-empiric management: evaluate at 48-72 hrs

• Response to treatment:
  • Clinical – temperature, control of sepsis, evaluation of source
  • Laboratory – WCC, CRP, culture results

• Assessment
  • Is there another non-infective cause?
  • Is antibiotic treatment still indicated?
  • If ongoing treatment indicated – consider early switch to oral
Limit durations of treatment

A very effective way to reduce selective pressure

Shorter duration treatments are feasible with:
• community pneumonia (3-5d)- extensive studies
• Intensive care unit pneumonia (7d)
• Localised UTI (3 days), UTI with sepsis (7-10d)
• Intra-abdominal sepsis with source controlled (1-7d),

Local guidelines need to specify recommended durations

Paterson-D et al. Strategies for Reduction in Duration of Antibiotic Use in Hospitalized Patients Clinical Infectious Diseases 2011: 52: 1232
Thank you!

Post graduate resources and access to online versions of current PNG STGs:
http://ldmic.net
http://aimed.net.au - Antimicrobial stewardship practical advice