Emerging Antimicrobial Resistance
A View (and response) from Down-Under

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Infectious Diseases & Microbiology Department, Austin Health
Department of Medicine, University of Melbourne, Australia

Hosted by Claire Kilpatrick
WHO Infection Control Global Unit

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Infection Control Global Unit - www.who.int/gpsc/en

Conflict of Interest Disclosures

Funding:
• Australian Commission on Safety & Quality in Health Care
• Australian National Health & Medical Research Council (NHMRC)
• Dept. of Health, Victoria, Australia
• Director, Hand Hygiene Australia
Overview

• The view from Mars
• Antimicrobial Resistance
  – Setting the scene for Australia
  – Current status – politics, resistance and prescribing
  – What is missing?
• New approaches
  – Building an IPC “fire-break”
  – New approaches to AMS
  – Re-assessing older agents
• The daunting future for Australia
  – What we can do about it

A brief summary of the problem

A view from Mars
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A brief summary of the problem

A view from Mars

- Pre-1940s – no Antibiotics
- Wonder drugs invented
- Within 70 years (2-3 human generations) – antibiotics misused
- Rapidly emerging multi-drug resistance
  - Gram+ves – MRSA, VISA, VRE, L-VRE
  - Gram-ves – CREs, colistin-resistant, etc
  - XDR-TB
  - Hypervirulent C. difficile
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- Wonder drugs invented
- Within 70 years (2-3 human generations) – misused
- Rapidly emerging multi-drug resistance
  - Gram+ve MSSA
  - Gram-ve VISA/VRSA
  - Candida
  - Clostridium difficile

This can’t be right!
No-one could be so completely stupid!

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Key problems - worldwide

- Weak regulatory systems & inability to enforce laws
- Ready availability of antibiotics
  - Over the counter sales
  - Internet sales
- Market and salary distortions for prescribers (MDs)
- Counterfeit drugs
- Poor laboratory diagnostic infrastructure
- Ready dissemination of MDR clones
  - Poor sanitation infrastructure in populous regions
  - Ready access to air travel
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Figure 5: Distribution of NDM-1-producing Enterobacteriaceae strains in Bangladesh, Indian, Pakistan, and the UK

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High rate areas for MDR Gram-negatives and Key Australian traveller destinations - 2012

- Very high risk - both ESBL and NDM Gram-negatives – food and drinking water
- High risk – ESBL Gram-negatives – mainly healthcare acquired
- Rapidly emerging high risk – ESBL Gram-negatives – contaminated food suspected
- Suspected risk – ESBL Gram-negatives – source uncertain


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Figure 1: The lag between an antibiotic being introduced to clinical use and the first appearance of resistance

Figure 2: Relationship between total antibiotic consumption and Streptococcus pneumoniae resistance to penicillin in 20 industrialised countries

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“One Health” approach

Responsive to the Threat of Antimicrobial Resistance

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Vision
A society in which antimicrobials are recognised and managed as a valuable shared resource, maintaining their efficacy so that infections in humans and animals remain treatable and communities continue to benefit from the advances that antimicrobials enable.

Goal
Minimise the development and spread of antimicrobial resistance and ensure the continued availability of effective antimicrobials.

Table 1: Australia’s list of priority organisms for human health

<table>
<thead>
<tr>
<th>Rationale</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact in both hospitals and the community</td>
<td>Enterobacteriaceae (principally Escherichia coli and Klebsiella species) Enterococcus species Escherichia coli Mycobacterium tuberculosis Neisseria gonorrhoeae Neisseria meningitidis Salmonella species Shigella species Streptococcus pneumoniae Staphylococcus aureus</td>
</tr>
<tr>
<td>Impact largely in hospitals</td>
<td>Acinetobacter baumanii complex Enterobacter cloacae/novartigenes Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Epidemiological and/or antimicrobial usage marker</td>
<td>Campylobacter jejuni/coli</td>
</tr>
<tr>
<td>Monitored through passive surveillance and elevated to targeted surveillance if threshold exceeded</td>
<td>Clostridium difficile Haemophilus influenzae type b Streptococcus agalactiae Streptococcus pyogenes</td>
</tr>
</tbody>
</table>

*WHO priority organisms for surveillance are listed.
Resistance Surveillance

AUSTRALIAN COMMISSION
ON SAFETY AND QUALITY IN HEALTH CARE

AURA
Antimicrobial Use and Resistance in Australia

What’s missing?

• AMR activities largely focused on surveillance and inappropriate antibiotic use

• Numerous effective infection control programs seen as HAI activities rather than as part of an AMR control strategy
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Australian AGAR Sepsis Outcome Studies 2013
Comparison to EARSS data 2012

Australian Group on Antimicrobial Resistance (AGAR)

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Klebsiella pneumoniae - % invasive isolates resistant to 3rd generation cephalosporins, 2012

AGAR BSI 2013

Klebsiella pneumoniae, % invasive isolates resistant to fluoroquinolones, 2012

AGAR BSI 2013

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What’s missing?
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What’s missing?

Information regarding the Clinical impact of AMR
Necessary to engage prescribers, the public and politicians

Improving Antimicrobial Stewardship

• Community usage – Pharmaceutical Benefits Scheme
• Hospital usage – NAUSP
• Practical stewardship issues

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Data source / methodology:
- Extracted from - Department of Human Services (DHS) Medicare pharmacy claims database and the DUSC database

Key Findings - Calendar year 2013:
- 45% of the Australian population (10,441,015 unique patients) were supplied at least one antibiotic through the PBS
  - 26,436,021 prescriptions supplied for systemic antibiotics
  - 29,227,581 prescriptions supplied for any antibiotic (including systemic & topical antibiotics)
- The most commonly supplied antibiotics were:
  - Amoxycillin (n=5,665,810)
  - Cephalexin (n=5,413,046)
  - Amoxycillin+clavulanic acid (n=4,512,149).
- The defined daily dose was calculated to be 22.8 DDD/1000/day
  - This is higher than the 2009 OECD average of 21.1

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Key Findings - 2013:

- $116.5 million in PBS/RPBS benefits was paid for antibiotics.

- For commonly used systemic antibiotics (amoxycillin, cephaalexin, roxithromycin and amoxycillin+clavulanic acid):
  - Repeats were ordered on the majority of prescriptions for cephaalexin, amoxycillin+clavulanic acid and roxithromycin.
  - Repeats were written on 40% of amoxycillin original prescriptions
  - The majority of repeats ordered were not dispensed

- Some original prescriptions and repeats were dispensed long after the date the prescription was written
  - This use may not be consistent with the original reason for the prescription

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Relationship of quinolone consumption and resistance in *E. coli*.
Durham K. *Eur J Clin Microbiol Inf Dis* 2010; 29, 353-356

- Restricted quinolone availability in humans and in food-producing animals → low fluoroquinolone resistance rates
- Conscious decision to avoid quinolones in clinical guidelines

**Control of Fluoroquinolone Resistance through Successful Regulation, Australia**

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 18, No. 9. September 2012

Van Boeckel, Ramanan Laxminarayan et al., TLID 2014

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The Australian Approach

Problem pathogens & impact on prescribing I

*S. pneumoniae*
- Penicillin resistance rare – clinically unimportant
- CAP – Rx of choice: Benzylpenicillin + doxycycline
- No fluoroquinolone use for CAP

*MRSA*
- Massive decline with National Hand Hygiene Initiative
- Some cMRSA – mostly sensitive to clindamycin and TMP-SMX
- Persistent MRSA bacteraemias – assessed for hVISA
- Minimal daptomycin use
- National system of SAB reporting – public disclosure

### Problem pathogens & impact on prescribing II

<table>
<thead>
<tr>
<th>VRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mostly vanB – susceptible to teicoplanin</td>
</tr>
<tr>
<td>High rates of vanB gene carriage in naturally occurring anaerobes</td>
</tr>
<tr>
<td>Most hospitals – faecal carriage screening in high-risk patients - isolation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. difficile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon – national reporting scheme</td>
</tr>
<tr>
<td>Minimal use of moxifloxacin and other fluoroquinolones; Federal approval required</td>
</tr>
<tr>
<td>Some increase in community rates - ?detection bias (incl PCR)</td>
</tr>
<tr>
<td>Metronidazole &gt; vancomycin &gt;&gt; fidaxomicin</td>
</tr>
<tr>
<td>Rarely - faecal transplantation - problems</td>
</tr>
</tbody>
</table>

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Graham et al. 2008 AAC 53:1195-7  
Young et al., 2007. JAC 59: 809-10

### Problem pathogens & impact on prescribing III

<table>
<thead>
<tr>
<th>MDR – Gram-negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main concern = returned travelers, incl. inter-hospital transfers</td>
</tr>
<tr>
<td>Discussion re. isolation and screening</td>
</tr>
<tr>
<td>Travelers - MDR salmonella and campylobacter common</td>
</tr>
<tr>
<td>Growing suspicion about contaminated imported foods</td>
</tr>
<tr>
<td>No. unexplained rural cases</td>
</tr>
<tr>
<td>Major impacts in some elective surgery:</td>
</tr>
<tr>
<td>Trans-rectal prostate biopsy</td>
</tr>
<tr>
<td>Colonic surgery</td>
</tr>
<tr>
<td>Questionnaires and pre-op faecal screening in some centres</td>
</tr>
</tbody>
</table>

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Creating an Infection Control “Fire-break”
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Hand Hygiene Australia

5 Moments for HAND HYGIENE

Australian NHHI participation – Private and Public
Period 1, 2009 – Period 3, 2016 – 940 sites

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### Organisation Types Summary

**Period 3, 2016**

<table>
<thead>
<tr>
<th>Organisation type</th>
<th>Organisations N (%)</th>
<th>Moments N (%)</th>
<th>Compliance* % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>893 (95%)</td>
<td>631529 (98.1%)</td>
<td>83.9 (83.9-84.0)</td>
</tr>
<tr>
<td>Dental/oral health clinic</td>
<td>27 (2.9%)</td>
<td>6736 (1%)</td>
<td>94.3 (93.7-94.9)</td>
</tr>
<tr>
<td>Community health service</td>
<td>14 (1.5%)</td>
<td>3113 (0.5%)</td>
<td>91.9 (90.9-92.8)</td>
</tr>
<tr>
<td>Long-term care facility</td>
<td>2 (0.2%)</td>
<td>466 (0.1%)</td>
<td>97.2 (95.3-98.5)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (0.4%)</td>
<td>2094 (0.3%)</td>
<td>86.6 (85.1-88.1)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>940</td>
<td>643,938</td>
<td>84.1 (84.0-84.2)</td>
</tr>
</tbody>
</table>

* Aggregate compliance with data from all organisations combined

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Hospital Types Summary

Period 3, 2016

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<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Acute hospitals</td>
<td>634 (71%)</td>
<td>545407 (86.4%)</td>
<td>83.7 (83.6-83.8)</td>
</tr>
<tr>
<td>Women's and children's hospitals</td>
<td>15 (1.7%)</td>
<td>22956 (3.6%)</td>
<td>84.2 (83.7-84.6)</td>
</tr>
<tr>
<td>Other acute specialised hospitals</td>
<td>13 (1.5%)</td>
<td>2907 (0.5%)</td>
<td>85.3 (84.0-86.6)</td>
</tr>
<tr>
<td>Same day hospitals</td>
<td>132 (14.8%)</td>
<td>26513 (4.2%)</td>
<td>85.4 (85.0-85.8)</td>
</tr>
<tr>
<td>Psychiatric hospitals</td>
<td>20 (2.2%)</td>
<td>5877 (0.9%)</td>
<td>87.0 (86.1-87.8)</td>
</tr>
<tr>
<td>Subacute and non-acute hospitals</td>
<td>49 (5.5%)</td>
<td>12132 (1.9%)</td>
<td>86.7 (86.1-87.3)</td>
</tr>
<tr>
<td>Outpatient hospitals</td>
<td>3 (0.3%)</td>
<td>128 (0%)</td>
<td>86.7 (79.6-92.1)</td>
</tr>
<tr>
<td>Unpeered hospitals</td>
<td>27 (3%)</td>
<td>15609 (2.5%)</td>
<td>86.5 (86.0-87.1)</td>
</tr>
</tbody>
</table>

* Aggregate compliance with data from all organisations combined.

Acute hospitals: Principal referral hospitals, Group A hospitals, Group B hospitals, Group C hospitals, Group D hospitals, Very small hospitals.
Women's and children's hospitals: Children's hospitals, Women's hospitals, Other women's and children's hospitals.
Psychiatric hospitals: Child, adolescent and young adult psychiatric hospitals, acute psychiatric hospitals, non-acute psychiatric hospitals, forensic psychiatric hospitals.

Hand Hygiene Performance: Hospitals


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Hand Hygiene Performance: Jurisdiction
Hospitals - Period 3, 2016

National Hand Hygiene Compliance Rates by HCW
535 Public facilities & 293 Private facilities
Period 3 (July-October) – 2014

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Other HHA initiatives

- Central HH database
- New direct-entry HH compliance App
  - i-Phones, other Smart-devices
Other HHA initiatives

- Central HH database
- New direct-entry HH compliance App
  - i-Phones, other Smart-devices
  - Benefits:
    - Reduces data management time by 50%
    - No duplicate data entry and errors
    - Mobile devices common and cheap
    - Flexible reporting options
    - Potential – NZ, Hong Kong, WHO
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Declining SAB rates in Australia

- Yearly incidence of HO-SAB – All hospitals
  - SAB
  - MSSA
  - MRSA

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Declining rates of healthcare-associated S. aureus bacteremia

Major reduction in national rates of healthcare-associated S. aureus bacteremia
Raw nos. - e.g. 2600 (2009-10) vs 1700 (2012)

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Other HHA initiatives

- Central HH database and data entry system
  - New direct-entry HH compliance App

- Adaptation of HHA system to become an AMR surveillance program
  - Linking HHA to AGAR

Establishing a National AMR Surveillance Program

- AMR surveillance using existing HHA database and mobile App technology
  - Aim: “Define the clinical impact of AMR”
  - Trial commenced last week – Melbourne and Perth
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Antibiotic Allergy and Antimicrobial Stewardship (AMS)

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Antibiotic Allergy and AMS

• Patient reported penicillin allergy prevalence 9%\(^1\)
• Patient reported antibiotic allergy prevalence 18-24%\(^1\)
• Penicillin allergy “labels” associated with excess length-of-stay, readmission, inappropriate antibiotic prescribing and antimicrobial resistance (inc. *Clostridium difficile* infection, MRSA, VRE)\(^2,3\)

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Comment: Allergy assessments and PCN skin testing can enhance use of first-line agents, but it is largely unstudied as a primary ASP intervention; however, ASPs should pro-

Austin Health Antibiotic Allergy Service

Targeted referral streams

AMS | ID Physicians | Allergists & immunologists | Other hospital physicians
---|---|---|---

ID/AMS assessment of patient antibiotic needs & microbiology

Antibiotic allergy testing (AAT)-AMS program
Multidisciplinary clinic: AMS/ID, allergy, pharmacy

Standardized testing protocols: Immediate vs. delayed allergies\(^1,2,3\)

Allergy testing outcomes

De-label | Re-label | Confirm-label
---|---|---

Patient feedback (written communication) | General Practitioner/Specialist (written communication)

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Re-assessing Older Antibiotics

Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia

Coline Pschirer,1 Karen Bush,2 William A. Craig,2 Niels Freund-Moller,3 M. Lindsay Grayson,5 John W. Mooten,6 John Purdy,7 Stephan Rebeschini,7 Inge E. Gysen,4,8 and the ESCMID Study Group for Antibiotic Policies
1Centre Hospitalier Universitaire de Nantes, Service d’Infectiologie et Université de Nantes, Saint-Antoine, Faculté de Médecine, France
2Biology Department, Indiana University, Bloomington, University of Wisconsin, School of Medicine and Public Health, Madison, Department of Clinical Microbiology, Indiana University, Indianapolis, Indiana, Infectious Diseases Division, Austin Health and Department of Medicine, University of Melbourne, Victoria, Australia; Department of Medical Microbiology, Radboud University Nijmegen Medical Centre and Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, the Netherlands; TIA Pathology, The University of Adelaide, SA, Australia; Repatriation University Hospital and Medical School, Sydney, Department of Medicine, Repatriation University Hospital Nijmegen Medical Centre and Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, the Netherlands; and 5Heineman University, Copenhagen, Belgium

Clinical Infectious Diseases 2012;54(2):269–74

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Re-assessing older agents

Fosfomycin

Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum β-lactamase producing, Enterobacteriaceae infections: a systematic review

Falgas et al. The Lancet ID 2010
Re-assessing older agents

Fosfomycin

Fosfomycin for the treatment of multidrug-resistant, including extended spectrum β-lactamase producing, Enterobacteriaceae infections: a systematic review

Mechanism of action:

- Bacterial cell wall inhibition – inactivation of enolpyruvate transferase =
  - Irreversible blockage of uridine diphosphate-N-acetylglucosamine condensation =
  - Blocks cell wall synthesis

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Fosfomycin

- Small molecule
- Broad spectrum of activity – esp. urinary pathogens (except PsA)
- Is the only representative of its class
- Target site unaffected by other ABx – no cross-class resistance

**Mechanism of action:**
- Bacterial cell wall inhibition – inactivation of enolpyruvate transferase =
  - Irreversible blockage of uridine diphosphate-N-acetylmuramic condensation =
  - Blocks cell wall synthesis

**Resistance – two mechanisms:**
- Chromosomal mutation = reduced transport into cell
- Plasmid-mediated – fosfomycin inactivation
- Overall rates of resistance – low (<5-10%)

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Fosfomycin

- Minimal serum protein binding
- Good tissue penetration
  - Soft tissue, bone, lung, heart valves, CNS
- PK/PD parameter – ? time-dependent (time above MIC)
- Oral preparations:
  - Fosfomycin-trometamol – Europe/USA/Australia
    - ~40% bioavailability (c.f. Fosfomycin-calcium - 10% bioavailability)
- IV Fosfomycin (fosfomycin disodium):
  - Availability
  - Dosage: 12-24 g/day in 2-4 divided doses (normal renal fn.)
  - Caution with doses >16 g/day – sodium overload and hypokalemia

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    - Caution with doses >16 g/day
    - Sodium overload and hypokalemia
  - Oral – 3g (fosfomycin-trometamol)
  - Safe
  - Effective against many MDR Gram-negatives

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**Is Fosfomycin a Potential Treatment Alternative for Multidrug-Resistant Gram-Negative Prostatitis?**

R. J. Goodwin, A. A. McKervey, A. G. Eiras, N. Ljungman, O. J. D. M. Edser, P. T. Zigmond, and A. G. Fournier

Department of Infectious Diseases and Department of Clinical Pharmacology, Austin Health, Heidelberg, Department of Surgery, University of Melbourne, Department of Medicine, University of Melbourne, Victoria, Australia

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Is Fosfomycin a Potential Treatment Alternative for Multidrug-Resistant Gram-Negative Prostatitis?

- Prospective, 26 healthy males, BPH = TURP
- Single 3g Fosfo, mean 9.5 hs pre-TURP
- Assessed plasma, urine and prostate levels (P/T zones, non-inflamed)
- Mean overall prostate levels: $6.5 \pm 4.9 \mu g/ml$ (R: 0.7-22.1)
  - 70% had concs $\geq 4 \mu g/ml$
- Therapeutic concentrations detectable up to 17 hs post-dose
- Mean prostate:plasma ratio $0.67 \pm 0.57$

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Figure 1. Mean fosfomycin prostate concentrations by time after single oral 3-g dose.

Optimal timing of oral fosfomycin administration for pre-prostate biopsy prophylaxis

Nathaniel J. Rhodes1,3, Bradley J. Gardiner1, Michael N. Neely2,5, Nathan Lawrentschuk2,4, Albert G. Fraunhofer1, Kelly M. Maxwell1, Teresa R. Zembower1 and Marc H. Scheetz1,4

1Department of Pharmacy Practice, Midwestern University, Chicago College of Pharmacy, Downers Grove, IL, USA; 2Department of Pharmacy, Northwestern Memorial Hospital, Chicago, IL, USA; 3Department of Infectious Diseases, Austin Health, Heidelberg, Victoria, Australia; 4Laboratory of Applied Pharmacokinetics and Bioinformatics, Saban Research Institute, Children's Hospital Los Angeles, Los Angeles, CA, USA; 5School of Medicine, University of Southern California, Los Angeles, CA, USA; 6Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia; 7Department of Clinical Pharmacology, Austin Health, Heidelberg, Victoria, Australia; 8Department of Surgery, Urology Unit, University of Melbourne, Melbourne, Victoria, Australia; 9Oliver Newton-John Cancer Research Institute, Austin Health, Heidelberg, Victoria, Australia; 10Department of Urology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; 11Division of Infectious Diseases, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

- Modelling – give oral fosfomycin 1-4 hs pre-prostate biopsy
- Avoid use if MIC >4 µg/ml

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Two plasma levels – 3g Fosfomycin

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Fosfomycin
Treatment of Prostatitis

Fosfomycin for Treatment of Prostatitis: New Tricks for Old Dogs

M. Lindsay Grayson,1,2 Renad Macesic,1 Janine Trevillyan,1,3
Andrew G. Ellis,2,4 Philip T. Zeglinski,2 Nicholas H. Hewitt,1
Bradley J. Gardiner,1 and Albert G. Fruman2,4

1Department of Infectious Diseases, Austin Health, 2Department of Medicine, University of Melbourne, 3Department of Infectious Diseases, Alfred Health, and
4Department of Clinical Pharmacology, Austin Health, Melbourne, Australia

(See the Editorial Commentary by Falagas and Rafaillidis on pages 1144–6.)

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Fosfomycin Treatment of Prostatitis

- Two patients with MDR *E. coli* prostatitis
- Failed multiple previous Rx, including prolonged meropenem
- Fosfomycin MIC 1 μg/ml (E-test)
- Treated with 3g oral fosfomycin daily (and 2x daily)
  - Patient 1 – 16 weeks
  - Patient 2 – 12 weeks
- Both cured 6 mths after completion of therapy
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Fosfomycin

- T
- F
- F
- T

Plasma fosfomycin level (μg/mL)

Days on therapy

3g po daily


Fosfomycin

- T
- F
- F
- T

Plasma fosfomycin level (μg/mL)

Days on therapy

3g po twice-daily


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Fosfomycin

Treatment of Prostatitis

Key considerations:
• What is the MIC? - probably needs to be ≤4 μg/ml
• Need to use 3g daily - can the patient tolerate this?
  – ? Try 3g twice-daily – but diarrhoea likely
• Treatment duration uncertain - ?12 weeks

Fusidic acid

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### Fusidic acid

- Used in Europe and Australia – many years
- Activity – *S. aureus, S. epidermidis*
- Inhibits protein synthesis by preventing translocation of elongation factor G (EF-G) from the ribosome
  - Steroid structure chemically related to cephalosporin P
    - Formed from *Cephalosporium acremonium*
  - Mode action explains its efficacy and lack of cross-resistance between fusidic acid and beta-lactams (e.g. MRSA)
  - “Steroid antibiotics” – due to resemblance to prednisolone; own class
  - *fusA* gene encodes for EF-G

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### Resistance – two mechanisms:
- *FusA* – reduced affinity with target ribosomal EF-G
- *FusB* – plasmid-mediated protection of EF-G from fusidic acid
  - now most prevalent
Fusidic acid

Dumb and Dumber—The Potential Waste of a Useful Antistaphylococcal Agent: Emerging Fusidic Acid Resistance in Staphylococcus aureus

Benjamin P. Hovdenak and M. Lindsay Grayson

Infectious Diseases Department, Austin Health, Heidelberg, and Departments of Microbiology and Epidemiology and Preventive Medicine, Monash University, and Department of Medicine, University of Melbourne, Melbourne, Australia

Clinical Infectious Diseases 2004;39:414-420

Figure 1. Number of methicillin-susceptible Staphylococcus aureus (MSSA) and methicillin-resistant S. aureus (MRSA) bloodstream isolates and percentage of those isolates that were fusidic acid (FA) resistant in the United Kingdom, 1989-2001. Prior to 1994, the numbers of MRSA isolates were very low, and percentage rates of FA resistance were variable. For those years, MRSA isolate numbers and the percentage that were FA resistant were as follows: 1990, 32 (1.6%); 1991, 74 (2.5%); 1992, 133 (6.9%); and 1993, 267 (10.9%). Based on data from 52.
Issues with Fusidic acid

- Need to use in combination to avoid resistance
  - Usually rifampicin
- Nausea - at some doses (esp. the elderly)
- Interactions – esp. statins
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  - e.g. prosthetic joint sepsis
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  - Usually rifampicin
- Nausea - at some doses (esp. the elderly)
- Interactions – esp. statins
- Useful for long-term oral suppression of MRSA
  - e.g. prosthetic joint sepsis
- In USA – Cempra Pharmaceuticals (CEM-102)
  - Low serum levels in combination with rifampicin

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Issues with Fusidic acid


- In USA – CEM-102
  - Low serum levels
  - Inconsistent with Australian experience
  - ? possible HLA impact
  - Large assessment underway with new FA assay

Overview

- The view from Mars
- Antimicrobial Resistance
  - Setting the scene for Australia
  - Current status – politics, resistance and prescribing
  - What is missing?
- New approaches
  - Building an IPC “fire-break”
  - New approaches to AMS
  - Re-assessing older agents
- The daunting future for Australia
  - What we can do about it

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The impending tsunami

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The impending tsunami

Contamination of the food chain

Ban resistant strains from food chain

No reliable treatment is available for humans infected with carbapenem-resistant Enterobacteriaceae (CREs; see Nature 499, 394–396; 2013). Because these antibiotic-resistant bacterial pathogens are already entering the food chain (J. Fisher et al. J. Antimicrob. Chemother. 68, 478–480; 2013) and can be transmitted through oral consumption (A. R. Manges and J. R. Johnson Clin. Infect. Dis. 55, 712–719; 2012), we call for a zero-tolerance ruling on CREs in retail food to stop the situation getting out of control. By 2007, it was estimated that more than 1,500 people in Europe had died from an...
Issues

• International trade rules allow testing for drug residues, not AMR pathogens

• Australia (2012) – Senate enquiry:
  – 341 tests on 194 seafood consignments – 96.4% passed
  – Positives – fluoroquinolones in prawns (VN)
  – ++ small testing program

or
Issues

- International trade rules allow testing for drug residues, not AMR pathogens
- Australia (2012) – Senate enquiry:
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Antibiotic Use in Australian Agriculture

- Chicken – yes (high)
- Pork – yes (moderate) - but ?decreasing
- Beef – yes – grain-fed beef (not pasture-fed)
- Lamb – no
- Dairy – yes (small) – impact uncertain
- Seafood – Australia none – but massive in Asia
- Crops – uncertain – the “new frontier”
Antibiotic Use in Australian Agriculture

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- Lamb – no
- Dairy – yes (small) – impact uncertain
- Seafood – Australia none – but massive in Asia
- Crops – uncertain – the “new frontier”
- ? new initiatives – e.g. insect farming

A new approach is needed in Australia

- Legislate to require foods to be tested for AMR pathogens as well as ABx residues
  - Test local produce and imports
- Reassess importation of some vaccines
- Greater focus on infection control in farms
- Include AMR and antibiotic use on all farming and food production agendas – a “One Health” approach
- Re-position Australian food as:
  - High quality and safe
  - Greater focus on quality vs price and quantity
Australian AMR Summit
29th June 2017

• What is Australia’s current progress re. AMR?
• Defining AMR progress according to WHO “4 pillars” of One Health:
  – Surveillance
  – IPC
  – Antimicrobial stewardship
  – Research & Development - vaccines, rapid diagnostics (POCTs), practical IPC initiatives, new drugs
• Need a “National AMR Co-ordinating Centre”

Conclusions

• AMR is no longer simply a health issue
  – It is also a social, economic and environmental issue
• Current situation re. new antimicrobial development is a major problem – will take a decade to fix
  – Need to reassess some older drugs
• We need to establish an infection control “fire-break”
  – Practical steps can be implemented - mandatory
• Reassess-restrict the use of antibiotics in agriculture
• Urgent need for improved national coordination

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What is in the Future without Antibiotics?

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