What’s hot in Infectious Diseases 2016

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Pathology North, Newcastle, NSW

Grand Rounds 1/3/16 Port Moresby
What’s on the menu?

1. New definitions for sepsis
2. Arboviruses on the move - Zika, Chika and Dengue
3. Apocalypse now – unintended consequences of antibacterial treatment and what we can do
Out with the old…
Lack of perfusion to organs is a key issue—produces hypoxia and lactic acidosis.

This is a view of the blood vessels under the tongue of two patients.

Sublingual ‘Orthogonal Polarization Spectral’ imaging.
Redefining sepsis: study cohorts

- Septic shock criteria—systematic review and validation across 18000 patient database
### Table 1. Variables for Candidate Sepsis Criteria Among Encounters With Suspected Infection

<table>
<thead>
<tr>
<th>Systemic Inflammatory Response Syndrome (SIRS) Criteria (Range, 0-4 Criteria)</th>
<th>Sequential Sepsis-related Organ Failure Assessment (SOFA) (Range, 0-24 Points)</th>
<th>Logistic Organ Dysfunction System (LODS) (Range, 0-22 Points)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Quick Sequential Sepsis-related Organ Failure Assessment (qSOFA) (Range, 0-3 Points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate, breaths per minute</td>
<td>$\text{Pao}_2/\text{FiO}_2$ ratio</td>
<td>$\text{Pao}_2/\text{FiO}_2$ ratio</td>
<td>Respiratory rate, breaths per minute</td>
</tr>
<tr>
<td>White blood cell count, $10^9$/L</td>
<td>Glasgow Coma Scale score</td>
<td>Glasgow Coma Scale score</td>
<td>Glasgow Coma Scale score</td>
</tr>
<tr>
<td>Bands, %</td>
<td>Mean arterial pressure, mm Hg</td>
<td>Systolic blood pressure, mm Hg</td>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>Administration of vasopressors with type/dose/rate of infusion</td>
<td>Heart rate, beats per minute</td>
<td></td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>Serum creatinine, mg/dL, or urine output, mL/d</td>
<td>Serum creatinine, mg/dL</td>
<td></td>
</tr>
<tr>
<td>Arterial carbon dioxide tension, mm Hg</td>
<td>Bilirubin, mg/dL</td>
<td>Bilirubin, mg/dL</td>
<td></td>
</tr>
<tr>
<td>Platelet count, $10^9$/L</td>
<td>Platelet count, $10^9$/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count, $10^9$/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output, L/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum urea, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time, % of standard</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 2. Distribution of Patient Encounters Over SIRS Criteria and SOFA, LODS, and qSOFA Scores Among ICU Patients and Non-ICU Patients With Suspected Infection in the UPMC Validation Cohort (N = 74454)

A. SIRS criteria

- ICU encounters (n = 7932)
- Non-ICU encounters (n = 66522)

B. SOFA score

- Encounters %
Sepsis syndrome definition changes

• ‘Sepsis’ defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
• For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. The predictive validity for in-hospital mortality of SOFA superior to SIRS score

“Severe Sepsis” – redundant term now
## SOFA score

### Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score<sup>a</sup>

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{PaO}_2/\text{FiO}_2$, mm Hg (kPa)</td>
<td></td>
<td>$\geq 400$ (53.3)</td>
<td>$&lt; 400$ (53.3)</td>
<td>$&lt; 300$ (40)</td>
<td>$&lt; 200$ (26.7) with respiratory support</td>
<td>$&lt; 100$ (13.3) with respiratory support</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets, $\times 10^3/\mu$L</td>
<td></td>
<td>$\geq 150$</td>
<td>$&lt; 150$</td>
<td>$&lt; 100$</td>
<td>$&lt; 50$</td>
<td>$&lt; 20$</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, mg/dL (μmol/L)</td>
<td></td>
<td>$&lt; 1.2$ (20)</td>
<td>$1.2-1.9$ (20-32)</td>
<td>$2.0-5.9$ (33-101)</td>
<td>$6.0-11.9$ (102-204)</td>
<td>$&gt; 12.0$ (204)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP $\geq 70$ mm Hg</td>
<td></td>
<td>MAP $&lt; 70$ mm Hg</td>
<td>Dopamine $&lt; 5$ or dobutamine (any dose)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Dopamine $5.1-15$ or epinephrine $\leq 0.1$ or norepinephrine $\leq 0.1$&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Dopamine $&gt; 15$ or epinephrine $&gt; 0.1$ or norepinephrine $&gt; 0.1$&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale score&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>$&lt; 6$</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL (μmol/L)</td>
<td></td>
<td>$&lt; 1.2$ (110)</td>
<td>$1.2-1.9$ (110-170)</td>
<td>$2.0-3.4$ (171-299)</td>
<td>$3.5-4.9$ (300-440)</td>
<td>$&gt; 5.0$ (440)</td>
</tr>
<tr>
<td>Urine output, mL/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$&lt; 500$</td>
</tr>
</tbody>
</table>

Abbreviations: $\text{FiO}_2$, fraction of inspired oxygen; MAP, mean arterial pressure; $\text{PaO}_2$, partial pressure of oxygen.

<sup>a</sup> Adapted from Vincent et al.<sup>27</sup>

<sup>b</sup> Catecholamine doses are given as $\mu$g/kg/min for at least 1 hour.

<sup>c</sup> Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.
### SOFA score

**Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score**

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<th>Score</th>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>$P_{a}O_2/\text{Fi}_O_2$, mm Hg (kPa)</td>
<td>≥400 (53.3)</td>
<td></td>
</tr>
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<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>≥150</td>
<td></td>
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<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, mg/dL (µmol/L)</td>
<td>&lt;1.2 (20)</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP ≥70 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
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</tr>
<tr>
<td>Glasgow Coma Scale score</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL (µmol/L)</td>
<td>&lt;1.2 (110)</td>
<td></td>
</tr>
<tr>
<td>Urine output, mL/d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Altered Consciousness Confusion Psychosis**

**Tachypnea $P_{a}O_2 < 70$ mm Hg $\text{Sa}_O_2 < 90\%$ $P_{a}O_2/\text{Fi}_O_2 < 300$**

**Jaundice $\uparrow$ Enzymes $\downarrow$ Albumin $\uparrow$ PT**

**Tachycardia Hypotension Altered CVP Altered PAOP**

**Oliguria Anuria $\uparrow$ Creatinine**

**Platelets $\uparrow$ PT/APTT $\downarrow$ Protein C $\uparrow$ D-dimer**

Abbreviations: $\text{Fi}_O_2$, fraction of inspired oxygen; MAP, mean arterial pressure; $P_{a}O_2$, partial pressure of oxygen.

*a* Adapted from Vincent et al.27

*b* Catecholamine doses are given as µg/kg/min for at least 1 hour.

*c* Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.
Septic shock

- Defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by:
  - **vasopressor requirement** to maintain a mean arterial pressure of 65 mm Hg or greater and
  - **serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia**. This combination is associated with hospital mortality rates greater than 40%.
Lactate predicts outcome and helps gauge response to treatment

Fig. 1 28-day in-hospital mortality risk stratified by blood pressure and serum lactate level
Caveats!

- Patient data are all exclusively from adults in high-income countries and primarily from USA.
- Utility of the definitions for resource poor regions and paediatric group unknown.
- Levels of patient monitoring, including lactate measurement and supportive care commonly used in USA not available in resource poor situation.
- Patient and infection-specific parameters largely ignored by the definitions and still require close consideration.
Epidemic and emerging disease alerts in the Pacific region as at 1 February 2016

Legend
- Red: Cases reported are increasing or peaking.
- Blue: Cases reported are decreasing or circulation is ongoing.
- Grey: Cases reported are decreasing or circulation is ongoing, awaiting confirmation of aetiology.

DEN: Dengue
ZIKV: Zika virus
ILI: Influenza-like illness
CHIK: Chikungunya

PACNET surveillance system
Zika: clinical features

- Typically mild, self-limiting illness
- ~80% infections asymptomatic
- Low-grade fever
- Maculopapular rash
- Arthralgia, myalgia
- Conjunctivitis, headache
- 4-7 days duration
Known Zika outbreaks in the Pacific 2012-present

<table>
<thead>
<tr>
<th>Year</th>
<th>Known outbreak-affected countries (dates)</th>
<th>Outbreak size (suspect and confirmed cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>French Polynesia (Oct 2013-May 2014&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>8,723 susp (30,000 estimated clinical visits)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2013</td>
<td>New Caledonia (Jan-Oct 2014&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>1,400 conf&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Cook Islands (Feb-May 2014&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>932 susp, 52 conf&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2014</td>
<td>Solomon Islands (Feb-May 2015&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Vanuatu (Feb-March 2015&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Fiji (August 2015&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Samoa (Sept 2015-ongoing&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>3 confirmed</td>
</tr>
<tr>
<td>2015</td>
<td>Tonga (Jan 2016-ongoing&lt;sup&gt;e&lt;/sup&gt;)</td>
<td>265 susp, 2 confirmed cases&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Samoa (ongoing)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PNG- 2014 – one case in Australian returned traveller
French Polynesia

- Review of birth data indicates an increase in the number of CNS malformations in children born between March 2014 and May 2015.
- Eighteen cases were reported including 9 microcephaly cases compared to the national average of 0 to 2 cases of microcephaly per year.
Guillain-Barre Syndrome

During the Zika virus outbreak in French Polynesia (2013-2014), 74 patients had presented neurological syndromes or auto-immune syndromes after the manifestation of symptoms consistent with Zika virus infection. Of these, 42 were classified as Guillain-Barré syndrome (GBS). Of the 42 registered GBS, 88% had signs and symptoms consistent with Zika virus infection (1, 2, 3).

Microcephaly in Brazil

• Between mid-2015 and Jan 30, 2016, 4783 suspected cases of microcephaly reported, including newborn and fetal losses. (expected incidence <200 per year)

• Of these, 1103 cases examined with 36% confirmed cases of microcephaly. Zika virus detected in 17 babies, including in two fetal losses.

Chikungunya

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td>Meningoencephalitis, encephalopathy, seizures, Guillain-Barré syndrome, cerebellar syndrome, paresis, palsies, neuropathy</td>
</tr>
<tr>
<td>Ocular</td>
<td>Optic neuritis, iridocyclitis, episcleritis, retinitis, uveitis</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Myocarditis, pericarditis, heart failure, arrhythmias, hemodynamic instability</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Photosensitive hyperpigmentation, intertriginous aphthous-like ulcers, vesiculobullous dermatosis</td>
</tr>
<tr>
<td>Renal</td>
<td>Nephritis, acute renal failure</td>
</tr>
<tr>
<td>Other</td>
<td>Bleeding dyscrasias, pneumonia, respiratory failure, hepatitis, pancreatitis, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), hypoadrenalism</td>
</tr>
</tbody>
</table>

*Adapted from Rajapakse et al.

- Severe disease- neonates, > 65 yo, esp if medical comorbidities present
Viral pathogens in children hospitalized with features of central nervous system infection in a malaria-endemic region of PNG

- Dengue cases – 2 with febrile convulsions (1 with S. pneumoniae, 1 with malaria); 1 case of fatal encephalitis

Distribution of Aedes mosquitoes

**Figure 3**
Map of the known distribution of *Aedes* (Stegomyia) mosquitoes, vectors of dengue and possible vectors of chikungunya and Zika viruses, Pacific Region as of beginning October 2014

- **Aedes albopictus**
- **Aedes polynesiensis**
- **Aedes hensilli**
- **Aedes rotundus**

*Aedes aegypti* present in most islands
**Aedes albopictus**

- Established in North Queensland and Torres Strait Islands but has been introduced on a number of occasions to NT, WA and NSW. An important pest species in Asia and other areas of the world where it has become established (northern, central and southern America, and Africa and Europe).

- A secondary vector of dengue viruses
Zika virus is an emerging pathogen that has recently been causing serious epidemics around the world. Cases of Zika virus disease were reported in Micronesia in 2007 and then in French Polynesia in 2013. In French Polynesia, Guillain-Barré syndrome was reported for the first time in a few patients following Zika virus infection. In Brazil, Zika virus was introduced in 2014 and was subsequently associated with cases of microcephaly. So far, an estimated minimum of 400,000 cases of Zika virus disease have been reported in 24 states in Brazil, although the number of cases could be far higher. Most cases are concentrated in the Pernambuco state, in the northeast region. Currently, many countries in South and Central America, besides Brazil, are reporting a high all discarded; thus, no other species were tested for the presence of Zika virus by these investigators. Lately, many other Aedes species have been surveyed for the detection of Zika virus, and thus far, Zika virus has been detected by RT-PCR or isolated from many mosquito species, human beings, and non-human primates.

Surprisingly, previous studies that have investigated the vector competence for Zika virus have neglected other mosquito species, such as Culex species, which are very abundant in the tropical areas where Zika virus has spread and have also transmitted arboviruses that are closely related to Zika virus, such as West Nile virus. Faye and colleagues reported a long list of mosquito species from which Zika virus strains

• Large possible list of non-Aedes potential vectors
• Relatively little research as yet
Zika: Laboratory diagnosis

- IgG and IgM serology and PCR
- No rapid antigen assays yet
- Viraemia short ~ 5 days (saliva, urine, blood)
- Initial/early serology may be negative
- Cross reactivity with dengue/ other flaviviruses
- Recent vaccination (yellow fever, Japanese encephalitis) may produce false Zika positive
- Confirm with neutralisation assay
Zika- sexual transmission?

- Two cases of probable sexual transmission of Zika virus from men to their sexual partners have been reported1,2.
- Two cases reported where Zika virus detected in semen, with detection up to nine weeks after symptomatic infection in one case3,4.
- In all instances, the men had had symptoms of infection though in one case transmission occurred in the period before symptoms.
Dengue in Papua New Guinea

- Large populations of the vectors *Aedes aegypti* and *Aedes albopictus* throughout PNG
- DEN type 2 outbreak 1971-1972
- Other dengue outbreaks 1976, 1983 and 1991; DEN types 1,2,3
- Possible DHF outbreak in Strickland Gorge, Southern Highlands 2001 (15% seropositivity)
- Importations of dengue acquired in PNG reported in North Queensland, Australia. 1999 - 2003: 51% of importations were from PNG; lesser numbers in 2004-2008
Contribution of Dengue Fever to the Burden of Acute Febrile Illnesses in PNG: An Age-Specific Prospective Study

**Madang province (IMR)**

- Outpatient clinics; 578 patients were enrolled, and 317 patients with negative rapid diagnostic test (RDT) for malaria were tested for dengue.
- Malaria was confirmed in 52% DF was diagnosed in 8% and 40% had neither diagnosis.
- Among the 317 malaria RDT-negative patients, 14% had DF.

Seroprevalence: Madang

**Figure 2.** Dengue IgG seroprevalence on acute samples; infant (< 1 year) seroprevalences were not shown because of existing maternal circulating antibodies.
Dengue study: PMGH

- Fever presentations at PMGH evaluated clinically and using NS1 dengue testing along with flavivirus serology
  - 16% dengue positive
  - 5% chikungunya positive

V Asigau : unpublished
Unintended consequences....
PNG Medical symposium 2015 - Antimicrobial resistance and PNG (Ferguson)

Presentation available – www.idmicnepal.net

A National Committee for Antimicrobial Resistance and Antibiotic Use should be established to oversee the monitoring of resistance among bacterial and other pathogens, improving to a minimum standard the microbiological facilities in all provincial hospitals, and overseeing antibiotic guidelines and stewardship. The Committee will be active and report annually. The Committee will contain representatives of CPHL, IMR, Pathology, Paediatrics, Medicine, Surgery, Pharmacy, and Disease Control Branch of the National Department of Health.
Why is antimicrobial resistance important?

1. Antimicrobial resistance kills - higher mortality in infections caused by 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
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%
These antibiotic surveys - common 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
Case report

- 16-yr boy admitted for the treatment of an acute flare of Crohn’s disease and a perirectal abscess. The patient was given ciprofloxacin 400 mg IV twice daily and metronidazole.
- Within 48 hours the patient became bradycardic. ECG showed a mildly prolonged Q-T interval (corrected Q-T interval, 486 msec) with heart rate of 42 beats/min. Antimicrobial therapy changed.
- The patient’s Q-T interval normalized within seven days of ciprofloxacin discontinuation. No further cardiac anomalies detected.

Prolonged QT syndrome

• Drugs including antimicrobials can cause prolongation of the QT interval, alone or in combination, potentially leading to fatal arrhythmias such as torsades des pointes
• When prescribing drugs that prolong the QT interval, the balance of benefit versus harm should always be considered
• Readouts from automated ECG machines are unreliable - QT interval should be measured manually
• Changes in heart rate influence the absolute QT interval. Heart rate correction formulae are inaccurate, particularly for fast and slow heart rates - use QT nomogram as a risk assessment tool to detect an abnormal QT interval

• Measure the QT interval length manually in 6 leads, usually: 3 limb leads: I, II and aVF; 3 chest leads: V2, V4 and V6
• Calculate the median QT and plot against the HR; if above the line = prolonged QT

Antimicrobials of concern

- Moxifloxacin > ciprofloxacin, gatifloxacin, levofloxacin,
- Azithromycin, erythromycin > clarithromycin
- Fluconazole, voriconazole
- Pentamidine
- Chloroquine
FDA and quinolones

• Concern about cardiac, musculoskeletal (tendon rupture) and peripheral neuropathy events.
• Nov 2015 joint meeting of two US Food and Drug Administration (FDA) advisory committees (antimicrobial drugs and drug safety) convened to discuss the relative risks and benefits in three largely minor conditions: acute bacterial sinusitis, acute bacterial exacerbations of chronic bronchitis, and uncomplicated urinary tract infections
• Concluded that quinolones should not routinely be used in these conditions
## Mortality and antibiotics

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>Mechanism</th>
<th>Mortality risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>Aplastic anaemia</td>
<td>1 in 20-40,000 courses</td>
</tr>
<tr>
<td>Betalactams</td>
<td>Anaphylaxis</td>
<td>1 in 50-66,000 courses</td>
</tr>
<tr>
<td>Trimethoprim (cotrimoxazole)</td>
<td>Hyperkalaemia from reduced distal renal tubular K secretion (trimethoprim)</td>
<td>In a population of patients more than 65 years on renin/AT inhibitors: 1 in 3,000 courses</td>
</tr>
<tr>
<td>Macrolides (eryth=azithro&gt;clarithromycin)</td>
<td>Prolonged QT – sudden death (torsades)</td>
<td>1 in 26,000 courses (33 studies involving 20,779,963 participants)</td>
</tr>
<tr>
<td>Quinolones (moxifloxacin&gt;&gt;ciprofloxacin)</td>
<td>Prolonged QT – sudden death (torsades)</td>
<td>Serious arrhythmia or sudden death: 1 in 25-50000 courses (possibly as high as 1 in 2-4000 courses with moxifloxacin)</td>
</tr>
</tbody>
</table>

[www.aimed.net.au](http://www.aimed.net.au)
• Classified as “Urgent Threat” by CDC in 2013
• Associated with excess mortality
• Extremely limited treatment options
The “Big Five” Carbapenemases of concern in Enterobacteriaceae*
“CPE” also termed “CRE”

NDM
KPC
VIM
IMP
OXA-48
(and variants)

* E. coli, Klebsiella, Enterobacter species etc
Carbapenemase genes are often transferrable on highly mobile plasmids

Multi-resistant – colistin used as a last resort drug
Apocalypse Now... plasmid - mediated colistin resistance

Generated in animal production in China (high colistin use) and documented spread to humans in 4 continents 2015-16.

Lancet Infectious Diseases 2016, January
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
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
Audit local prescribing behaviour

• Study how antibiotics are being used in your unit
• Document diagnosis, drugs, dosage, duration and indication
• Assess appropriateness, bug-drug mismatch, compliance against guidelines; involve other local experts including your microbiologist in the analysis
• Drive change – reduce or eliminate pointless use, develop and implement local guidelines
National Antimicrobial Prescribing Survey (NAPS) - Australia

- Online point prevalence survey tool survey with advanced reporting capability
- Available to PNG Hospitals; can be targeted for certain drugs or syndromes/situations

www.naps.vicniss.org.au
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 SOFA score (organ 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
Local antibiograms in preparation (courtesy Dr J Joseph)

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Post-empiric management: evaluate at 48-72 hours

• 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!
22. Spicer PE, Taufa T, Benjamin AL. Scrub typhus (Orientia tsutsugamushi), spotted fever (Rickettsia australis) and dengue fever as possible causes of mysterious deaths in the Strickland George area of Southern Highlands and West Sepik Provinces of Papua New Guinea. PNG Med J 2007; 50(3-4): 172-83
24. Hanna JN, Ritchie S.A. An apparent recent decline in importations of Dengue from PNG into North Queensland. CDI. Vol 33, 1, 2009