Antimicrobial resistance in low- and middle-income countries

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the problem
Where we were...

THE EFFECT OF ANTIBIOTICS (PENICILLIN, AUREOMYCIN, AND TERRAMYCIN) ON THE FATALITY RATE AND INCIDENCE OF COMPLICATIONS IN PNEUMOCOCCIC PNEUMONIA. A COMPARISON WITH OTHER METHODS OF THERAPY

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NNT
• 10-19 yrs ~100
• 70+ yrs ~2

Am J Med Sci 1951;222:396
Today: KPC global impact
Where we are going…
Deaths from antimicrobial resistance, 2050

- North America: 317,000
- Europe: 390,000
- Africa: 4,150,000
- Latin America: 392,000
- Asia: 4,730,000
- Oceania: 22,000

~10 million deaths per annum

https://amr-review.org
What about mortality from sepsis?

27 population-based studies, 7 HICs

Am J Respir Crit Care Med 2016 193 3 259–272
Estimate of global sepsis burden

- Sepsis incidence
  - $437 (334-571) / 10^5$ person-yr (RECENT DATA)
  - 31.5 million cases per annum

- Severe sepsis incidence
  - $270 (176-412) / 10^5$ person-yr (RECENT DATA)
  - 19.4 million cases per annum

Deaths: 5.3 million per annum
Resistance is an old phenomenon

Diverse genes for resistance to β lactam, tetracycline, glycopeptide abx
Resistance starts at birth, develops with antibiotic pressure

- Polymicrobial, variably antimicrobial-resistant, commensal microbiome in infancy
- Darwinian selection from antibiotic pressure
  - Human use affects commensal flora and pathogens
  - Confounding by
    - illness severity
    - pathogen-host interactions
    - Other factors
  - Agricultural and veterinary use
Antibiotics

Sites of action

Agents that inhibit DNA synthesis:
- Fluoroquinolones

Agents that inhibit RNA polymerase:
- Rifampin

Mechanisms of resistance

Permeability barriers

Efflux pump

Antibiotic target modification:
- Altered penicillin-binding proteins
- Altered DNA gyrase

Agents that bind to ribosomes and inhibit protein synthesis:
- Aminoglycosides
- Tetracyclines
- Macrolides
- Clindamycin
- Chloramphenicol
- Linezolid

Inactivating enzymes:
- β-lactamase
- Aminoglycoside-modifying enzymes

Agents that inhibit cell wall synthesis:
- Penicillins
- Cephalosporins
- Carbapenems
- Glycopeptides (vancomycin)

Bacterial cell wall
Resistance transfer between bacteria

Transduction
Bacteriophages (viruses that infect bacteria) mediate transfer of DNA between bacteria via transduction, whereby DNA from a donor bacterium is packaged into a virus particle and transferred into a recipient bacterium during infection.

Conjugation
The mechanism of gene transfer responsible for the most concerning aspects of antimicrobial resistance. A sex pilus (small tube) forms between two bacterial cells through which a plasmid is transferred from one to the other.

Transformation
Some bacteria are able to take up free DNA from the environment and incorporate it into their chromosome.

Free DNA

plasmid

bacteriophage

Lancet 2016; 387: 176–87
Timeline of resistance

Proc R Soc B 2014;281:20141861
solutions
Framework: increase antimicrobial access AND limit resistance

Lancet 2016; 387: 285–95
Mechanisms and drivers of antimicrobial resistance

Lancet 2016;387:176–187
Vaccination to decrease demand

(a) Streptococcus pneumoniae incidence rate
(per 100,000 children under age 5)

Key:
- <1000
- 1000 - <2000
- 2000 - <3000
- ≥3000

(b) Pneumococcal conjugate vaccine (PCV)
global implementation status

Key:
- Yes
- For high risk groups
- Will be implemented soon
Better sanitation in LMICs:
↑ life expectancy AND ↓ antibiotic consumption

https://amr-review.org/
Antimicrobial resistance associated with antibiotic exposure

n=19
z=0.84 (0.62–0.94)
p<0.0001
Current antibiotic consumption highest in HICs

Lancet Inf Dis 2014;14:742
Growth in antibiotic consumption highest in LMICs

Lancet Inf Dis 2014;14:742
Reasonable studies of HCAI in LMICs
High prevalence and incidence vs. HICs

AMR generally not measured

Lancet 377:228-41
AMR challenges in LMICs

• Infection
  – Higher incidence
  – Higher prevalence of AMR bacteria

• Antibiotics
  – Higher growth in antibiotic prescribing
  – Lack of prescription controls
  – Counterfeit drugs
  – Purchasing power for newer antibiotics lower

• Hospital
  – Poor IPC
  – Laboratory capacity limited and expensive
Relevance of AMR in ICUs

• Highest concentration of antibiotic usage
  – 51% with infection
  – 71% on antibiotics (vs. 30-40% on hospital wards)

• Sick patients cohoorted
  – Ripe environment for cross-contamination and transmission of resistant organisms

• Higher risk of death

JAMA 2009;302:2323-2329
# MDR bacteremia in Thailand

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Community-acquired bacteraemia (CAB)</th>
<th>Healthcare-associated bacteraemia (HCAB)</th>
<th>Hospital-acquired bacteraemia (HAB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR <em>Staphylococcus aureus</em></td>
<td>94/1176 (8%)</td>
<td>73/259 (28%)</td>
<td>222/446 (50%)</td>
</tr>
<tr>
<td>MDR <em>Enterococcus spp</em></td>
<td>0/176 (0%)</td>
<td>0/49 (0%)</td>
<td>4/117 (3%)</td>
</tr>
<tr>
<td>MDR <em>Escherichia coli</em></td>
<td>1177/3382 (35%)</td>
<td>288/494 (58%)</td>
<td>252/403 (63%)</td>
</tr>
<tr>
<td>MDR <em>Klebsiella pneumoniae</em></td>
<td>146/1010 (14%)</td>
<td>71/196 (36%)</td>
<td>301/455 (66%)</td>
</tr>
<tr>
<td>MDR <em>Pseudomonas aeruginosa</em></td>
<td>13/286 (5%)</td>
<td>10/103 (10%)</td>
<td>45/179 (25%)</td>
</tr>
<tr>
<td>MDR <em>Acinetobacter spp</em></td>
<td>125/449 (28%)</td>
<td>58/115 (50%)</td>
<td>374/501 (75%)</td>
</tr>
</tbody>
</table>

![Map of Thailand](image)
Impact of MDR bacteremia

B

- *Staphylococcus aureus*: 1.5 (0.9–2.7)
- *Enterococcus spp*: NA
- *Escherichia coli*: 1.7 (1.1–2.5)
- *Klebsiella pneumoniae*: 1.5 (0.9–2.8)
- *Pseudomonas aeruginosa*: 1.0 (0.3–3.7)
- *Acinetobacter spp*: 5.3 (2.3–12.1)
- Subtotal (I²=51%, P=0.09): 1.9 (1.2–2.8)

C

- *Staphylococcus aureus*: 1.9 (1.3–2.9)
- *Enterococcus spp*: 1.1 (0.1–8.4)
- *Escherichia coli*: 1.8 (1.1–2.7)
- *Klebsiella pneumoniae*: 1.1 (0.7–1.7)
- *Pseudomonas aeruginosa*: 1.2 (0.6–2.5)
- *Acinetobacter spp*: 5.6 (3.6–8.9)
- Subtotal (I²=83.4%, P<0.001): 1.9 (1.2–3.2)

Odds ratio for mortality
Potential approaches in the ICU

- **Infection control**
  - Hand hygiene
  - Active surveillance
  - Contact precautions
  - Cohorting

- **Patient level**
  - Skin decolonization with chlorhexidine
  - Oral chlorhexidine
  - SDD
  - (no) ulcer prophylaxis

- **Antibiotic**
  - Stewardship teams
  - ‘rotation’

- **Diagnostics**
  - Limit decision to start or duration of empiric therapy
  - Microbiology laboratory
Multifaceted interventions: education and stewardship

• Before-after study in single centre in Thailand

• Results
  – **Less** inappropriate abx Rx, 640 vs. 400/1000 admissions
  – **Reduced** 3rd gen cephalosporins, glycopeptides
  – More cefazolin and fluoroquinolones
  – **Decreased** resistance rates
    • MRSA
    • *E coli, K pneumoniae*
    • Acinetobacter

Clin Infect Dis 2006; 42:768–75
Multifaceted interventions: contact isolation, stewardship, hand hygiene

- Before after study in single centre in Korea
Multifaceted interventions: contact isolation, stewardship, hand hygiene

- Before after study in Korea
Chlorhexidene baths

• Systematic review of 2 trials + 5 time series
• 6 of 7 studies used washing
• Results
  – Decreased MRSA transmission (n=3)
  – Decreased MRSA colonization (n=1)
  – Decreased VRE carriage and bacteremia (n=1)
  – NO data on resistant gram negatives

Intensive Care Med 2012;38:931–939
How to study?

• Observational (e.g. before-after)
  – biased estimates of treatment effect
  – Would be upgraded for dramatic effects that are unlikely realistic

• RCTs
  – Cluster: most interventions ICU-based
  – Outcome of AMR also ICU-based
    • changes require that all patients be exposed to intervention
Challenges, irrespective of design

• Access to antibiotics (i.e., financial coverage)
• Access to genuine supply
• Ascertainment of the outcome
  – Need laboratory capacity even if not studied as an intervention
Challenges for RCTs

• Interactions
  – effect of any one strategy may be contingent on the use of other strategies

• Heterogeneity of effects across subgroups
  – baseline resistance rates
  – type of bacteria
  – burden of comorbidity (as a marker of previous antimicrobial exposure)

• Purpose
  – implementation strategies (hand hygiene) vs effectiveness (others)
Approach to effectiveness vs implementation

<table>
<thead>
<tr>
<th>Study Characteristic</th>
<th>Hybrid Trial Type 1</th>
<th>Hybrid Trial Type 2</th>
<th>Hybrid Trial Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research aims</td>
<td>Primary aim: determine effectiveness of a clinical intervention</td>
<td>Coprimary aim*: determine effectiveness of a clinical intervention</td>
<td>Primary aim: determine utility of an implementation intervention/strategy</td>
</tr>
<tr>
<td></td>
<td>Secondary aim: better understand context for implementation</td>
<td>Coprimary aim: determine feasibility and potential utility of an implementation</td>
<td>Secondary aim: assess clinical outcomes associated with implementation trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>intervention/strategy</td>
<td></td>
</tr>
<tr>
<td>Research questions</td>
<td>Primary question: will a clinical treatment work in this setting/these patients?</td>
<td>Coprimary question*: will a clinical treatment work in this setting/these patients?</td>
<td>Primary question: which method works better in facilitating implementation of a</td>
</tr>
<tr>
<td>(examples)</td>
<td>Secondary question: what are potential barriers/ facilitators to a treatment’s</td>
<td>Coprimary question: does the implementation method show promise (either alone</td>
<td>clinical treatment?</td>
</tr>
<tr>
<td></td>
<td>widespread implementation?</td>
<td>or in comparison with another method) in facilitating implementation of a clinical</td>
<td>Secondary question: are clinical outcomes acceptable?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment?</td>
<td></td>
</tr>
</tbody>
</table>
The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Platform Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope</td>
<td>Evaluating efficacy of multiple agents in a heterogeneous population; explicitly assumes treatment effects may be heterogeneous</td>
</tr>
<tr>
<td>Duration</td>
<td>Potentially long-term, as long as there are suitable treatments requiring evaluation</td>
</tr>
<tr>
<td>No. of treatment groups</td>
<td>Multiple treatment groups; the number of treatment groups and the specific treatments may change over time</td>
</tr>
<tr>
<td>Stopping rules</td>
<td>Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s)</td>
</tr>
<tr>
<td>Allocation strategy</td>
<td>Response-adaptive randomization</td>
</tr>
<tr>
<td>Sponsor support</td>
<td>The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination</td>
</tr>
</tbody>
</table>

JAMA 2015; 313: 1629
Bringing together elements from recent thinking about trials

- Outcome measurements to assess both effectiveness vs. implementation
- Continuous timeline
- Combinations of interventions possible
- Stopping rules for interventions that prove effective
- Adaptive randomization
  - Unclear if will work in a cluster trial
Summary

- Antimicrobial resistance is not a new problem, but much worse now
- Much of antibiotic growth (= pressure) will come in LMICs
- The ICU is at the leading edge of AMR development
- Many interventions may reduce AMR
- Innovations in trial design needed to account for complex and interacting interventions
Thank you

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