Antibiotic Resistance: How do we manage?

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Disclosures

Speaker bureau, advisory boards, research grants

• Astra-Zeneca
• Pfizer
• Sandoz
• Edwards Life sciences
• Hexor
• Fresenius Kabi
• Aspen
• Abbvie
• Abbot
• Pharmadynamics
• Litha
June 1944

“His penicillin will save more lives than war can spend”

September 1994

ANTIBIOTICS

A FADED MIRACLE?

2020 ?

ANTIBIOTICS

We Won the Battle
For Now...
Global burden: MDR Pathogens
700 000 Deaths/annum
2050: 10 million deaths/annum

HAIs
US: 4.5-7 Billion USD
UK: 1 Billion GBP

Welcome Trust, 2014
Bull WHO 2015;93:66
AMR: Global Action Plan

• US National action plan
• European initiative
• Chennai Declaration
• Chinese Declaration
• Thailand Antibiotic smart use
• South African AMR background document

US aims to cut antibiotic use in new five year plan to combat antibiotic resistant bacteria

White house, Washington, 2015
AMR : Core principles

Coordinated policy aligned with global strategy + stakeholders’ commitment

Access

Conserve antibiotic use

Innovation

Appropriate agent available when required (LMIC), not incentive driven or OTC

Reduce need & Responsible use (surveillance, prevent infections, infection control, prescriptions)
Medical and non-medical sector

Diagnostics
Agents
Vaccines
Infection control
Antibiotic stewardship - Community - Hospital
Therapeutic strategies (dual antibiotics)
Antibiotic cycling
Rapid diagnostics
New antibiotics
Vaccines
Bacteriophage therapy
Non-medical use - Veterinary - Aquaculture
Genomics
Immunotherapy
Delivery systems
Governance, Education, Communication
Health Systems Strengthening & legal Framework
Global Coordination
Potential Strategies
Access
Surveillance

HOW EFFECTIVE?
Antibiotic stewardship programs

• Antibiotic exposure and resistance risk
• Systematic reviews
  – 43 trials (≈ antibiotic use or AMR)
  – 24 trials (≈ antibiotic use)
• Vary
• Benefits due to AMS?
  – Superimposed policies
  – Infection control
  – Staff ratios
  – Bed occupancy
• Essential

Stewardship
• Team
• Surveillance
• Formulary restriction
• Choice, dose, duration (PK, PD)
• De-escalate
• Education
• Infection control

Feazel LM et al. J Antimicrob Ther 2014s
De-escalation

- Neonates
  - Reduced likelihood of resistance
- Adults
  - Resistance data: paucity
- Consensus
Antibiotic cycling

- Clinical and mathematical models
- Evidence
- Utility in current practice
Infection control and screening

- Infection control measures 30-40%
- In the pipeline?
  - Copper coating of surfaces
  - Silver coating of devices and surfaces
  - Safety, efficacy and cost
- Routine surveillance/screening
  - Staff
  - Patients
New agents: New antibiotics

- Antibiotic RnD stagnant
- 70 substances
- GNB
  - Very few
  - New mechanism of action
- Revitalize RnD
  - Tax incentives
  - Co-funding
  - Longer patents
  - Fast tracking RnD processes

New agents

• Efflux inhibitors
• Quorum sensing inhibitors
• Anti-virulence strategies
• Antibiotic adjuvants
• Biological agents
  – Immune modulators
  – Igs
Rapid diagnostics

• Diagnostic uncertainty
• Need
  – Early diagnosis
  – Early organism ID
  – Susceptibility
• Biomarkers
  – CRP and PCT
  – Multiplex panels
Rapid diagnostics

• Cultures

• Newer and investigational
  – Proteins (MALDI-TOF MS)
  – DNA
    • FISH
    • PCR
  – New generation sequencing

• Issues
  • Cost
  • Accuracy (false positive)
  • Time (6-8 hours)
  • Susceptibility
Vaccines: Their appeal

• Reduce antibiotic use
  – Prevent bacterial infections
  – Prevent viral infections (inappropriate antibiotics)
  – Secondary infections avoided
  – Herd immunity
Vaccines impact

• Reduced bacterial infections
  – Vaccinated
  – Non-vaccinated
• Cost effective (LMIC)

Cost-effectiveness and economic benefits of vaccines in low- and middle-income countries: A systematic review

Sachika Drzawa*, Andrew Mirelman*, Meghan I. Stack*, Damian G. Walker*, Dean S. Levine*

Effect on antibiotic use

• Children PCV7
  – US: 100 vaccines → avoids 35 antibiotic prescriptions
  – 1.4m fewer antibiotic prescriptions/year
  – Herd immunity: fewer adult hospitalizations for invasive Strep infections
• Adults H1N1
  – Fewer adult pneumonia hospitalizations
Vaccine developments

• Adjuvant vaccines
• New adjuvants
  - TLR Agonists
• Vaccines: MDR (GPB and GNB)

De Frasco L. Nat Biotech 2008;26:484
Vaccines : Limitation

**Adult Pneumococcal Vaccination Rates**

<table>
<thead>
<tr>
<th>Location</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>~ 60%</td>
</tr>
<tr>
<td>Nottingham, England</td>
<td>32% - 60%</td>
</tr>
<tr>
<td>Catalonia, Spain</td>
<td>62.5%</td>
</tr>
<tr>
<td>France</td>
<td>21.9%</td>
</tr>
<tr>
<td>Catalonia, Spain</td>
<td>38.6% - 53.1%</td>
</tr>
<tr>
<td>Slovakia</td>
<td>6.3% - 17.6%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>75%</td>
</tr>
</tbody>
</table>

**Barriers to Immunization**

- Burden of disease
- Misperceptions related to risk of disease
- Misunderstanding of risk groups
- Concern about lack of efficacy
- Guidelines
- Inadequate reimbursement
- Side effects
- Cost
- Fear of needles
- Inconvenience
- Lack of support
- Infrastructure
- Registries
Bacteriophage therapy

Applications: Humans

- Prophylaxis
- Treatment
- Biofilm
  - Polysaccharide depolymerase
  - *P. aeruginosa, Serratia, Enterobacter (Pantoea)*
- Evidence
  - > 100 trials
  - Prophylactic and therapeutic
  - With and without antibiotics
  - Efficacy of 55-90% - local and systemic infections (superior with IV route)
  - Includes MDR organisms

Bacteriophages: Issues

- Critically ill
  - IV route and neutralizing antibodies
- Immunocompromised
  - Immunosuppression
- Dose
- Multiple dosing
- Resistance
- Industry

Antibiotics: Agriculture and Aquaculture

• Volume of antibiotics
  – 50-80% of antibiotic consumption

• Animal health and growth promotion

• Resistance association

• Global action plan includes high level engagement

NDoH, South Africa 2015
Global threat: Where do we stand?

AMR: Global threat

Action plan
Political pressure
High level commitment

[Table/Fig-1]: Approaches for combating antimicrobial resistance
Std.: Standard, R & D Research and Development, OTC: Over-the-Counter

Combat Antimicrobial Resistance

- Increased Collaboration
- Rational Drug Use
- Infection Control & Prevention
- Antimicrobial Surveillance
- National Policy
- Essential Drug List
- AMR Committee
- New AMR Programmes
- Std. Treatment Guidelines
- Hand Hygiene
- Immunization Coverage
- Ban on OTC Antibiotic
- Educate Motivate
- R & D Drug/Vaccine

Global threat: Where do we stand?

- CDC
- Global Action Plan on AMR
- World Health Organization
- World Health Assembly

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