AMR and its impact on neonatal sepsis

Stephen Baker

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Me

- Professor of Microbiology at the University of Oxford
- I live and work in Ho Chi Minh City in Vietnam
- I have been based here for 11 years
- I am involved in projects all over Asia
- My group uses clinical data, genomics and classical microbiology to study the biggest regional issues
- My focus is one enteric (Gram negative) bacteria
discovery phase, where rapid diagnostics would enable the development and clinical adoption of pathogen-targeted antibiotics. The wide genetic diversity of pathogenic bacteria (16) has been an obstacle to the development of broad-spectrum drugs. Molecules that target individual pathogens of particular importance should be easier to identify and optimize for selectivity and toleration, and more rapid to develop in targeted patient populations. One such pathogen could be *Acinetobacter baumanii*, which is often resistant to current treatments and is associated with high mortality rates (17). Such narrowly targeted drugs should be premium priced as they would be used to treat a small number of patients with serious, otherwise untreatable infections (18).

Rapid molecular diagnostics paired with dependency wards in South Asia (6). These outbreaks were caused by particularly virulent variants, which induced a rapid-onset bacteremia resulting in a 75% mortality rate in the infected children. The presence of NDM-1 within an already broadly antimicrobial-resistant and highly virulent strain severely restricted the treatment options, with

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**INFECTIONOUS DISEASE**

**A return to the pre-antimicrobial era?**

The effects of antimicrobial resistance will be felt most acutely in lower-income countries

By Stephen Baker*3

After many years out of the limelight, antimicrobial resistance (AMR) in bacteria is firmly back on the international political and scientific agenda (1, 2). The potential impact of AMR on hospital-acquired bacterial infec-
DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW

Key:
- O: COMMONLY ACT AS BACTERIOSTATIC AGENTS, RESTRICTING GROWTH & REPRODUCTION
- X: COMMONLY ACT AS BACTERICIDAL AGENTS, CAUSING BACTERIAL CELL DEATH

**6-LACTAMS**
- MOST WIDELY USED ANTIBIOTICS IN THE NHS
- All contain a beta-lactam ring
  - **EXAMPLES**: Penicillins (shown), such as amoxycillin and flucloxacillin; Cephalosporins such as cefazolin.
- **MODE OF ACTION**: Inhibit bacteria cell wall biosynthesis

**AMINOGlycosides**
- FAMILY OF OVER 20 ANTIBIOTICS
- All contain aminoglycoside substructures
  - **EXAMPLES**: Streptomycin (shown), neomycin, kanamycin, paromomycin.
- **MODE OF ACTION**: Inhibit the synthesis of proteins by bacteria, leading to cell death
- No longer a first-line drug in any developed nation due to increased resistance and worry about safety

**CHLORAMPHENICOL**
- COMMONLY USED IN LOW INCOME COUNTRIES
- Distinct individual compound
  - **EXAMPLES**: Chloramphenicol (shown), tobramycin, gentamicin.
- **MODE OF ACTION**: Inhibit the synthesis of proteins by bacteria, leading to cell death

**GLYCOPEPTIDES**
- COMMON DRUGS OF LAST RESORT
- Consist of carbohydrate linked to a peptide formed of amino acids
  - **EXAMPLES**: Vancomycin (shown), teicoplanin.
- **MODE OF ACTION**: Inhibit bacteria cell wall biosynthesis

**ANSAMYCINS**
- CAN ALSO DEMONSTRATE ANTIVIRAL ACTIVITY
- All contain an aromatic ring bridged by an aliphatic chain
  - **EXAMPLES**: Geldamycin (shown), rifamycin, naphthyridinum.
- **MODE OF ACTION**: Inhibit the synthesis of RNA by bacteria, leading to cell death

**STREPTOGAMINS**
- TWO GROUPS OF ANTIBIOTICS THAT ACT SYNERGISTICALLY
  - Combination of two structurally differing compounds, from groups related A & B
  - **EXAMPLES**: Pristinamycin IA (shown), Pristinamycin B
- **MODE OF ACTION**: Inhibit the synthesis of proteins by bacteria, leading to cell death

**SULFONAMIDES**
- FIRST COMMERCIAL ANTIBIOTICS WERE SULFONAMIDES
- All contain the sulfonamide group
  - **EXAMPLES**: Prontosil, sulfanilamide (shown), sulfadiazine, sulfisoxazole.
- **MODE OF ACTION**: Do not kill bacteria but prevent their growth and multiplication. Cause allergic reactions in some patients.

**TETRACYCLINES**
- BECOMING LESS POPULAR DUE TO DEVELOPMENT OF RESISTANCE
- All contain 4-adjacent cyclic hydrocarbon rings
  - **EXAMPLES**: Tetracycline (shown), doxycline, minocycline, oxytetracycline.
- **MODE OF ACTION**: Inhibit synthesis of proteins by bacteria, preventing growth.

**MACROLIDES**
- SECOND MOST PRESCRIBED ANTIBIOTICS IN THE NHS
- All contain 16, 15, or 16-membered macrocyclic ring
  - **EXAMPLES**: Erythromycin (shown), clarithromycin, azithromycin.
- **MODE OF ACTION**: Inhibit protein synthesis by bacteria, leading to cell death

**OXAZOLIDINONES**
- POTENT ANTIBIOTICS COMMONLY USED AS ‘DRUGS OF LAST RESORT’
- All contain 2-oxazolidinone somewhere in their structure
  - **EXAMPLES**: Linezolid (shown), posizolid, tolzolid, tasoxacrine.
- **MODE OF ACTION**: Inhibit synthesis of proteins by bacteria, preventing growth.

**QUINOLONES**
- RESISTANCE EVOLVES RAPIDLY
- All contain fused aromatic rings with a carbonylic acid group attached
  - **EXAMPLES**: Ciprofloxacin (shown), levofloxacin, trovafloxacin.
- **MODE OF ACTION**: Interfere with bacteria DNA replication and transcription

**LIPopePTIDES**
- INSTANCES OF RESISTANCE RARE
- All contain a lipid bonded to a peptide
  - **EXAMPLES**: Daptomycin (shown), surfactin.
- **MODE OF ACTION**: Disrupt multiple cell membrane functions, leading to cell death
The issues with neonatal sepsis

• Changes in AMR can be observed in this syndrome
• Many colonizing organisms are AMR and can cause infection
• Mom is likely the major source of infection
• Empirical treatments are failing
• These issues are worse in LMICs in Asia
• MDR, XDR and pan resistant organisms are now common
• We are already living in an era with untreatable infections
The main players

- *Klebsiella pneumoniae*
- *Escherichia coli*
- *Acinetobacter Baumannii*
- *Enterobacter cloacae*
- *Various staphylococcus species*

- It is a complex and rapid disease, empirical treatment is often the only option
A high-resolution genomic analysis of multidrug-resistant hospital outbreaks of *Klebsiella pneumoniae*

Hao Chung The\(^{1,\dagger}\), Abhilasha Karkey\(^{2,\dagger}\), Duy Pham Thanh\(^{3}\), Christine J Boinett\(^{3}\), Amy K Cain\(^{3}\), Matthew Ellington\(^{3,4}\), Kate S Baker\(^{3}\), Sabina Dongol\(^{2}\), Corinne Thompson\(^{1,5}\), Simon R Harris\(^{3}\), Thibaut Jombart\(^{6}\), Tu Le Thi Phuong\(^{1}\), Nhu Tran Do Hoang\(^{1}\), Tuyen Ha Thanh\(^{3}\), Shrijana Shretha\(^{2}\), Suchita Joshi\(^{2}\), Buddha Basnyat\(^{2}\), Guy Thwaites\(^{1,5}\), Nicholas R Thomson\(^{3,7,\dagger}\), Maia A Rabaa\(^{1,8,\dagger}\) & Stephen Baker\(^{1,5,7,1,\dagger}\)
Klebsiella outbreaks

- Our hospital in Nepal has had several outbreaks on the NICU
- In May 2012 there was major outbreak of Klebsiella
- It affected several wards
- Cefotaxime resistance with variable susceptibility to Carbapenems
- Recrudescence in November 2012, 2014 and 2016
- 75% mortality rate
**Klebsiella outbreaks**

- Disease was associated with an almost pan resistant Klebsiella
- The organisms could be detected in the stool of mothers
- It had variable response to colistin
- It was associated with a new type of plasmid and new capsular variant
- Virulent MDR *Klebsiella* strains are rare but increasing
- Many outstanding questions; but what next?
So where are we now?

• We have sustained surveillance for neonatal sepsis in Kathmandu
• We are starting to understand *Klebsiella* and its virulence potential and AMR capacity
• Community carriage is a daunting prospect
• Mothers and babies get sampled longitudinally
• Assess empirical therapy and limit transmission
• Measure “AMR” and its role in disease and mortality
• Ongoing study in Vietnam
Neonatal sepsis study; Vietnam

- What is the role of AMR in outcome of neonatal sepsis?
- 18 month study in a single centre
- 530 children recruited
- 420 organisms isolated
- Characterize organisms and their susceptibility profile
- Genome sequence key organisms
- Relate genome composition to outcome (15% mortality)
So what do we need?

- A better understanding of the biology of neonatal sepsis
- A measure of the impact of AMR
- A standardized database to assess organism dynamics
- Better diagnostic approaches
- Combination empirical treatment
- Improved infection control
- Standardized outcome/organism data
How do we tackle AMR?

- New drugs?
- Repurposing and/or phenotypic reversion of older drugs
- Testing of combinations
- Alternative approaches
  - Vaccination of mom
  - Therapeutic antibodies
  - Disease control strategies
  - Narrow spectrum treatments with diagnostics
Thank you and goodnight