In 2035, will all bacteria be multiresistant?

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Faculty Disclosure

Advisory Boards
- MERCK USA, Bayer Europe, MSD Europe, Clinigen UK, Cardeas USA, Virogates Denmark, Cempra USA, Tetraphase USA, Gilead UK

Lectures fees
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- Asian-Pacific Society of Infectious Diseases
In 2035, will all bacteria be multiresistant? 
The story of antibiotics

- Discovery of penicillin, streptomycin, chloramphenicol and tetracycline
  - Early during 20th century
- After 7 years of penicillin’s first use
  - 50% of hospital *Staphylococcus aureus* isolates were resistant
- In 2004, > 70% of pathogenic bacteria were resistant to at least one antibiotic
  - MDR (Multi-Drug Resistant)
    - The pathogen is resistant in at least one agent in ≥3 antimicrobial categories
  - XDR (Extensively – Drug Resistant)
    - The pathogen is resistant to all classes except 1 or 2 (usually colistin)
  - PDR (Pan-Drug Resistant)
    - The pathogen is resistant to all classes of antibiotics

Magiorakos AP et al. CMI 2012 Mar;18(3):268-81
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Resistance mechanisms

- Mutation
- Acquisition of foreign DNA

- Environmental factors and fitness of the resistant strain
- Spontaneous
- Independent of antibiotic presence
- A function of the bacterial and of the antibiotic

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Resistance mechanisms

The main resistance mechanisms include

- Inactivation via hydrolysis
- Alteration of bypassing the drug target
- Preventing access of the drug to the target sites making the cells unrecognizable to the antibiotic
- Active efflux out of the cell via membrane-bound efflux transporters

Penesyan A et al. Molecules 2015;20:5286-8
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Biofilm

Resistomes = diverse natural ecosystems (human gut, soil etc)

- a. contain genes able to confer resistance to antimicrobials
- b. lead to matrices of polysaccharide / extracellular DNA complex
- c. biofilm development

- promotes cellular resistance due to a high mutation rate (>100 times higher than plaktonic cells)
- faster development of antibiotic-resistant mutants
- horizontal gene transfer acquisition
- spread of resistance determinants

Flemming HC. Nat Rev Microb 2010;8623-33, Debabov D. Appl Biochem Microb 2013;49;655-71
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Resistance mechanisms of *Pseudomonas aeruginosa*


Figure was produced by M. Akova
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Endemic, Epidemic, Pandemic, Syndemic

- **Endemic**
  An infection is maintained in a population without the need for external inputs.

- **Epidemic**
  The rapid spread of *infectious disease* to a large number of people in a given population within a short period of time, usually two weeks or less.

- **Pandemic**
  An *epidemic* of *infectious disease* that has spread across a large region (*f.i.* multiple continents, or worldwide).

- **Syndemic**
  The aggregation of two or more concurrent or sequential *epidemics* or disease clusters in a population with biological interactions, which exacerbate the *prognosis* and *burden of disease*.
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#### Outbreaks

<table>
<thead>
<tr>
<th>What is outbreak?</th>
<th>How to approach outbreaks?</th>
</tr>
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<tbody>
<tr>
<td>An increase over the background or 'endemic' rate of infection in a geographic area (f.i ICU) with a particular microbe or of a specific type of infection such as SSI or BSI.</td>
<td></td>
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<tr>
<td>Only 8% of BSI are related to an outbreak</td>
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<tr>
<td>▪ confirmation</td>
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<tr>
<td>▪ multidisciplinary team</td>
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<td>▪ literature search</td>
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</table>

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Approaching an outbreak

**Molecular epidemiology**

I. **Genes**
   - *f.i.* VIM-1 type (gene cassette)
   - or VIM-2 type base element and number of nucleotides

II. **Integrons**
   - different structure suggests a different evolution process rather than a transfer various *transposons*

III. **Plasmids**

**Rapid detection of resistance**

**PCR**
- highly sensitive and specific method
- unavailable for daily use in many laboratories

**New Chromogenic medium CHROMagar KPC**
- CHROMagar orientation supplemented with agents that inhibit the growth of gram positive / gram-negative carbapenem-sensitive bacteria.

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*Samra et al, J Clin Microb 2008, p. 3110–3111*
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Finding the source

1. **Patient care items**
   medications, enteral feeds, equipment

2. **Person-to person transmission**

3. **Environmental reservoirs**
   Contamination of infusions, enteral feeds, medications (during manufacture) is referred as "intrinsic" contamination
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Clinically Relevant Considerations in Resistance

- **Polyclonal epidemiology**
  - usually associated with antibiotic use

- **Clonal epidemiology**
  - may be amenable to infection control

The type of resistance observed may help determine the measures that need to be taken to manage resistance

Single-center, 2-year study (Guideline to restrict cephalosporin use)
Main outcome: to reduce the incidence of CAZ-resistant *Klebsiella* colonization and infection.
- 80% reduction in cephalosporin use
  - 44% reduction in CAZ-resistant *K. pneumoniae* (p<0.01)
  - 71% reduction in CAZ-resistant *K. pneumoniae* in the ICU
  - 88% reduction in the surgical ICU (p<0.001)
- Imipenem-resistant *P. aeruginosa* retained sensitivity to *β*-lactams, quinolones, aminoglycosides

CAZ = ceftazidime

In vitro results from 15 Brooklyn hospitals showed that:

□ Cephalosporin use correlated with emergence of a MDR clone of *Acinetobacter* spp.

□ Ribotyping revealed that a single clone accounted for 62% of the samples and was isolated from patients at all 15 hospitals.

□ Improved infection control is an important component of managing such outbreaks.

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Resistance from the community

Person-to-person transmission in PUBLIC places → Antibiotic resistance within the community setting ← Person-to-person transmission in PRIVATE places

Selection pressures from:
- exposure to antibiotics
- ingestion of antibiotic-treated food-stuffs
In 2035, will all bacteria be multiresistant? The environment of ICU

Potential reservoirs of infection - mattresses and pillows = KNOWN

HOWEVER....... ..all the bed components have to be adequately decontaminated to minimise the risk of cross-infection

Creamer et al, Journal of Hospital Infection (2008) 69, 8e23
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The environment of ICU

× represents VRE culture positive sites

Contaminated surfaces increase cross-transmission
The hand of an intensivist in the agar
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Colonization and Infections

- Colonized patients
  - people who carry bacteria without evidence of infection
  - Infection usually from bacteria that colonize patients

- Bacteria that colonize patients
  - can be transmitted from one patient to another by the hands of healthcare workers

Bacteria can be transmitted even if the patient is not infected
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Hands flora

“Transient” flora

✓ Enterobacteriaceae
  ▪ *E. coli*
  ▪ *Klebsiella* spp
  ▪ *Proteus* spp
  ▪ *Serratia* spp
  ▪ *Enterobacter* spp

✓ *Pseudomonas* spp
✓ *Acinetobacter* spp
✓ MRSA
✓ VRE

“Resident” flora

☐ CoNS
☐ Micrococci,
☐ *Propionibacterium* spp
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Hand hygiene: Methods and Techniques

- **Handwashing**
  - Washing hands
    - plain soap/water

- **Antiseptic handwash**
  - Washing hands
    - water and soap or detergents containing an antiseptic agent

- **Alcohol-based handrub**
  - Rubbing hands
    - alcohol-containing preparation

- **Surgical hand hygiene / antisepsis**
  - Handwashing
    - alcohol-based handrub before operations

Guideline for Hand Hygiene in Health-care Settings. MMWR 2013;51:RR-16
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Hand hygiene: the right solution

Good

Better

Best

Plain Soap

Antimicrobial soap

Alcohol-based handrub
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Hand hygiene: the right way

avoiding the recontamination
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We still use antibiotics……………..

…………..and will do so

Despite antibiotic restriction practices
- large scale consumption continues to occur
- the consumption patterns favor the use of parenteral agents, already having highest rates of resistance (β-lactams, macrolides, quinolones)

Demographic characteristics favor increasing utilization rates of antibiotics
- In 2013, the leading cause of deaths among young children were LRTIs and diarrheal diseases among older children

Pressures on antibiotic utilization will continue to occur

Kyu HH et al. JAMA Peiatr 2016
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Newer antibiotics

Newer antibiotics
Have been developed to treat existing antibiotic-resistant pathogens

However,

- a KPC-producing *Klebsiella pneumoniae* isolate has been reported to ceftazidime-avibactam (MIC 32/4µg/ml) in a patient without prior treatment with this antibiotic

- Relebactam (imipenem +relebactam) did not improve the activity of imipenem against *Acinetobacter baumanii*
  - MICs for *ampC* and *blaOXA-51* producing strains were unchanged ➔ No activity of relebactam
  - Imipenem + relebactam has not been released for clinical use

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Alternative therapies

New delivery methods
- Nebulization
- Encapsulation of antibiotics

Vaccines

Monoclonal Antibodies

Modulation of immune response

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New delivery methods

**Nebulization**
- Colistin and aminoglycosides
- Heterogeneous dosage, regimens and indications
- Lack of standardization and broad experience
- ESCMID ➔ salvage Rx in MDR under a strict protocol

**Encapsulation methods**
- Improve the drug diffusion
- Protect the drug from undesired degradation
- Control drug release
- Increase uptake in the infected sites
- Anionic liposomes, polyacid nanoparticles, water-soluble oligosaccharide conjugates, polymeric nanocomposites, solid nanoparticles
- Ciprofloxacin, meropenem, aminoglycosides (already encapsulated)
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Vaccines – Monoclonal Antibodies

**Vaccine IC43**
- a recombinant outer membrane protein (Opr)
- no significant difference was found in *P. aeruginosa* infection rates although it was associated with a lower mortality rate
- Despite evident immunogenicity between days 7 and 14, *P. aeruginosa* infection occurred prior to the development of IgG immune response.

**Monoclonal Antibodies**
- KB001, a pegylated anti-PcrV MA fragment to the type III secretion system (TTSS) of *P. aeruginosa* involved with the release of exotoxins
- IgY avian polyclonal antibody
- MEDI3902 binding to PcrV and Psl mediating cytotoxicity
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Modulation of immune response

- **Inhibitors of quorum sensing**
  - activity against biofilm formation and secretion of virulence factors
  - none of them has been evaluated in clinical practice
  - only macrolides were associated with a trend to prevent VAP and reduction of quorum sensing–regulated virulence factors activation

- **Neutralization of virulence effectors**
  - target the ability of bacteria to evade the immune system

- **Gallium**
  - an iron mimetic, inhibits *in vitro P. aeruginosa* growth and biofilm formation

- **Bacteriophages**
  - prevent damage to normal flora
  - do not infect the eukaryotic cells
  - are not associated with rapid proliferation inside the host bacteria.
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Conclusions

We don’t know if in 2035 will all bacteria be multiresistant but for sure antibiotic resistance

a. will continue to emerge to existing as well as to new agents
b. will escalate over time
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Resistance increases MIC!!!

- Mortality, ICU length of stay, Cost

- Infection control to minimize infections rates, resistance emergence and spread
- Hand hygiene
- Treatment of outbreaks
- Surveillance
- Adequate Use of antibiotics

the other meaning of MIC