Antibiotic Resistance: Causes, Consequences & Local Scene

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Antibiotic Resistance – A Global Problem

- MRSA
- PRP
- ESBL
- VRE
- MBL
- VISA
- VRSA

- 1961 Penicillin
- 1967 3rd gen cephalosporin
- 1983 Vancomycin
- 1986 Carbapenem
- 1988 Vancomycin and teicoplanin
- 1996 Vancomycin and teicoplanin
- 2002
Driving force for antibiotic resistance

- Inadequate national commitment to a comprehensive and coordinated response, ill-defined accountability and insufficient engagement of communities;
- Weak or absent surveillance and monitoring systems;
- Inadequate systems to ensure quality and uninterrupted supply of medicines;
- Inappropriate and irrational use of medicines, including in animal husbandry;
- Poor infection prevention and control practices;
- Depleted arsenals of diagnostics, medicines and vaccines as well as insufficient research and development on new products.
Resistance to antibacterial agents

• Antibiotic resistance either arises as a result of innate consequences or is acquired from other sources

• Bacteria acquire resistance by:
  – mutation: spontaneous single or multiple changes in bacterial DNA
  – addition of new DNA: usually via plasmids, which can transfer genes from one bacterium to another
  – transposons: short, specialised sequences of DNA that can insert into plasmids or bacterial chromosomes
Mechanisms of antibacterial resistance (1)

- Structurally modified antibiotic target site, resulting in:
  - reduced antibiotic binding
  - formation of a new metabolic pathway preventing metabolism of the antibiotic
Structurally modified antibiotic target site

Antibiotics normally bind to specific binding proteins on the bacterial cell surface

Cell wall

Interior of organism
Structurally modified antibiotic target site

Antibiotics are no longer able to bind to modified binding proteins on the bacterial cell surface.

Antibiotic

Modified target site

Cell wall

Changed site: blocked binding

Interior of organism
Mechanisms of antibacterial resistance (2)

- Altered uptake of antibiotics, resulting in:
  - decreased permeability
  - increased efflux
Altered uptake of antibiotics: decreased permeability

Antibiotic

Porin channel into organism

Cell wall

Interior of organism
Altered uptake of antibiotics: decreased permeability

Antibiotic

New porin channel into organism

Cell wall

Interior of organism
Altered uptake of antibiotics: increased efflux

Antibiotic

Porin channel through cell wall

Cell wall

Interior of organism
Altered uptake of antibiotics: increased efflux
Mechanisms of antibacterial resistance (3)

• Antibiotic inactivation
  – bacteria acquire genes encoding enzymes that inactivate antibiotics

• Examples include:
  – $\beta$-lactamases
  – aminoglycoside-modifying enzymes
  – chloramphenicol acetyl transferase
Antibiotic inactivation

Cell wall

Antibiotic

Enzyme

Binding

Target site

Interior of organism
Antibiotic inactivation

Antibiotic inactivation occurs within the interior of an organism. Antibiotics and enzymes interact at specific target sites within the cell wall, leading to the inactivation of the antibiotic. The diagram illustrates the binding of enzymes to target sites, resulting in the inactivation of antibiotics.

Cell wall

Interior of organism
Antibiotic inactivation

- Antibiotic
- Enzyme
- Target site
- Cell wall
- Antibiotic destroyed
- Antibiotic altered, binding prevented
- Interior of organism
## Major classes of antibiotics & resistance mechanisms

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Mechanism of action</th>
<th>Major resistance mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactams</td>
<td>Inactivate PBPs (peptidoglycan synthesis)</td>
<td>• β-lactamases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Low affinity PBPs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Efflux pumps</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Bind to precursor of peptidoglycan</td>
<td>• Modification of precursor</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Inhibit protein synthesis (bind to 30S subunit)</td>
<td>• Modifying enzymes (add adenyl or Phosphate)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Inhibit protein synthesis (bind to 50S subunit)</td>
<td>• Methylation of rRNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Efflux pumps</td>
</tr>
<tr>
<td>(Fluoro)Quinolones</td>
<td>Inhibit topoisomeraseases (DNA synthesis)</td>
<td>• Altered target enzyme</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Efflux pumps</td>
</tr>
</tbody>
</table>

PBPs penicillin-binding proteins
β-Lactamases: Classification

Serine enzymes
- Group C
  - AmpC
  - Cephs Inhib-R
- Group A
  - TEM/SHV
  - Pens, Cephs Inhib-S
- Group D
  - OXA
  - Pens, esp Oxa Inhib-R/S
Metallo (Zn) enzymes
- Group B
  - IMP/VIM
  - Carbapenems Inhib-R

Modified Bush–Jacoby–Medeiros
Classification of $\beta$–Lactamases

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Substrate profile</th>
<th>Molecular Class</th>
<th>Inhibitor</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cephalosporinase</td>
<td>C</td>
<td>Oxa</td>
<td>AmpC, MIR-1</td>
</tr>
<tr>
<td>2a</td>
<td>Penicillinase</td>
<td>A</td>
<td>Clav.</td>
<td>S.aureus</td>
</tr>
<tr>
<td>2b</td>
<td>Broad spectrum</td>
<td>A</td>
<td>Clav.</td>
<td>TEM-1/2, SHV-1</td>
</tr>
<tr>
<td>2be</td>
<td>Extended spectrum</td>
<td>A</td>
<td>Clav.</td>
<td>TEM 3-29, TEM46-104 SHV2-28, CTX-M types</td>
</tr>
<tr>
<td>2br</td>
<td>Inhibition resistant</td>
<td>A</td>
<td>-</td>
<td>TEM 30-41 (IRT1-12)</td>
</tr>
<tr>
<td>2c</td>
<td>Carbenicillinase</td>
<td>A</td>
<td>Clav.</td>
<td>PSE-1</td>
</tr>
<tr>
<td>2d</td>
<td>Oxacillinase</td>
<td>D</td>
<td>(Clav.)</td>
<td>OXA-1 (OXA-2 &amp;-10 derived ESBL)</td>
</tr>
<tr>
<td>2e</td>
<td>Cephalosporinase</td>
<td>A</td>
<td>Clav.</td>
<td>FPM-1 P. vulgaris, CepA B. fragilis.</td>
</tr>
<tr>
<td>2f</td>
<td>Carbapenemase</td>
<td>A</td>
<td>Clav.</td>
<td>IMI-1, NmcA, Sme 1-3</td>
</tr>
<tr>
<td>3</td>
<td>Metallo-enzyme</td>
<td>B</td>
<td>-</td>
<td>S.maltophilia</td>
</tr>
<tr>
<td>4</td>
<td>Penicillinase</td>
<td>-</td>
<td>-</td>
<td>B.cepacia</td>
</tr>
</tbody>
</table>
Antimicrobial features of ESBLs

• Inhibited by $\beta$-lactamase inhibitors
• Usually confer resistance to:
  – first-, second- and third-generation cephalosporins (eg ceftazidime)
  – monobactams (eg aztreonam)
  – carboxypenicillins (eg carbenicillin)
• Varied susceptibility to piperacillin/tazobactam
• Typically susceptible to carbapenems
• Often clinically and/or microbiologically non-susceptible to fourth-generation cephalosporins
Antimicrobial features of carbapenem resistance

• Natural resistance is chromosomally mediated
  – naturally occurring carbapenemases

• Acquired resistance is plasmid-mediated, involving various mechanisms
  – most commonly by carbapenemases (especially in Gram-negative bacteria)
  – reduced affinity of target PBPs
  – decreased membrane permeability (Gram-negative bacteria)
  – active efflux pumps

• Mechanisms can co-exist and vary by pathogen
Antimicrobial features of carbapenem resistance: carbapenemases

- Carbapenemases are a major source of acquired resistance in Gram-negative bacteria
- Belong to three different molecular classes of β-lactamases:
  - class B metallo-enzymes (eg IMP, VIM, NDM-1)
  - class D oxacillinases (OXA-23 to OXA-27)
  - class A clavulanic acid-inhibited enzymes (eg SME, NMC, IMI, KPC)

Antimicrobial features of MRSA

• Mechanism involves altered target site
  – new penicillin-binding protein — PBP 2' (PBP 2a)
  – encoded by chromosomally located mecA gene
• Confers resistance to all β-lactams
• Cross-resistance common with many other antibiotics
• Gene carried on a mobile genetic element — staphylococcal cassette chromosome mec (SCCmec)

Antimicrobial features of VRE

- Development is slow due to very complex gene mechanisms:
  - Alters pentapeptide precursor end sequence from D-alanyl-D-alanine to D-alanyl-D-x, where x is lactate, serine or other amino acid
  - Or produces (vanY) tetrapeptide that cannot bind vancomycin

![Vancomycin resistance gene sequence diagram]

- Detects glycopeptide; switches on other genes
- Produces D-Lac
- Produces D-Ala-D-Lac
- Cleaves D-Ala-D-Ala
- *Cleaves D-Ala and D-Lac from end chain
- Exact role? Teicoplanin resistance?
Antimicrobial features of VISA

• Mechanism not fully understood, but a combination of:
  – increased quantities of PBPs causing extracellular trapping
  – altered cell wall proteins reducing permeability
Antimicrobial features of VRSA

• Mechanism due to acquisition by conjugative process of vanA from enterococci
### MDRO situations in HA hospitals 2009 - 2010

<table>
<thead>
<tr>
<th>Incidence</th>
<th>MRSA BSI</th>
<th>VRSA</th>
<th>VRE</th>
<th>ESBL+ NR</th>
<th>CRE/ CRE</th>
<th>PCR +ve</th>
<th>CRA/ MDRA</th>
<th>CRPA/ MRPA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2009</strong></td>
<td>0.17</td>
<td>No</td>
<td>0.2%</td>
<td>20-25%</td>
<td>0.05 to 0.07%</td>
<td>NA</td>
<td>39%</td>
<td>4.75%</td>
</tr>
<tr>
<td></td>
<td>/1000 acute bed days</td>
<td></td>
<td>Sporadic outbreaks in hospitals</td>
<td></td>
<td>/ NA</td>
<td></td>
<td>MDRA= 2.6 to 4%</td>
<td>MRPA= 0.1%</td>
</tr>
<tr>
<td><strong>2010</strong></td>
<td>0.15</td>
<td>No</td>
<td>0.4%</td>
<td>20-25%</td>
<td>0.19%</td>
<td>?</td>
<td>?</td>
<td>4.62%</td>
</tr>
<tr>
<td></td>
<td>/ 1000 acute bed days</td>
<td></td>
<td>(3 outbreaks involved 28 patients)</td>
<td></td>
<td>/ 13 cases</td>
<td></td>
<td>MDRA= 2.1%</td>
<td>MRPA= 0.1%</td>
</tr>
<tr>
<td><strong>Trend</strong></td>
<td>Decreasing (12%↓ cf 2009; 21%↓ cf 2007)</td>
<td>No</td>
<td>Slightly increasing</td>
<td>stable</td>
<td>Low but increasing</td>
<td>MDRA: Slightly decreasing</td>
<td>stable</td>
<td></td>
</tr>
</tbody>
</table>

MRPA=concomitant R to Imipenem, Ceftazidime, Amikacin and Ciprofloxacin
MDRA= concomitant R to Fluoroquinolones, Aminoglycosides, Cephalosporins and BL/BLase inhibitor combinations

Courtesy of CICO Office, HA
• **Streptococcus pneumoniae:**
  – Penicillin intermediate susceptibility or resistance
    Ip et al. JCM 1999
  – Widespread macrolide resistance
    Ip M et al. AAC 2001
  – Emerging fluoroquinolone resistance
    Ho PL et al. JAC 2000
    Ho PL et al. EID 2001

• **Enterobacteriaceae:**
  – Up to 20% of E. coli and 9% of Klebsiella spp. from urine specimens at out-patient settings are ESBL producers
    Data from PHLSB, CHP

• **Nisseria gonorrhoeae:**
  – Established fluoroquinolone resistance
    Kam KM et al. STD 1996
  – Emerging ceftibuten resistance
    Lo JY et al. AAC 2008

• **TB:**
  – Annual rate ~ 90/100000 population
  – MDR-TB ~ 1%
  – XDR-TB ~ 0.1%
• TB:
  – Annual rate ~ 90/100000 population
  – MDR-TB ~ 1%
  – XDR-TB ~ 0.1%
Antibiotic use, resistance, treatment failure and healthcare burden: a vicious circle

Increase in antibiotic use

Increase in resistant strains

Ineffective empiric therapy
  • increased morbidity
  • more antibiotics

Limited treatment alternatives
  • more antibiotics
  • increased mortality

Increased use of healthcare resources

Increased hospitalisation
  • more antibiotics
Trends in Development of New Antibacterials

*p^2 = 0.99

*p = 0.007 by linear regression

New antibacterial agent ≡ new molecular entity (NME) with antimicrobial properties, administered for systemic infection; topical agents, immunomodulators excluded

Edwards J, ICAAC, 2003