Antibiotic Pharmacodynamics: Relation to Antimicrobial Resistance

Valeria Conti
Dept. Medicine, Surgery and Dentistry
“Scuola Medica Salernitana”
vconti@unisa.it
Chemotherapy definition (Paul Ehrlich, 1910)

The term chemotherapy refers to a wide range of chemical substances both natural and synthetic with a selective toxicity towards prokaryotic and eukaryotic cells responsible for:

Infections
Tumors
Immune system disorders

Based on the targets we distinguish chemotherapy:

- **ANTIMICROBIAL**
- **ANTIBLASTIC**
- **IMMUNOMODULANT**
The antibiotic era starts with the Penicillin discovery

The first discovered antimicrobial compound was penicillin (Flemming, 1929) a $\beta$-lactam antibiotic. After this very important discovery, antibiotics were used to treat human infections and for prophylactic purpose and are also widely used in agricultural practices.
The introduction of penicillin led to a dramatic decline of the mortality rate due to infectious diseases.
Before and after: causes of death in industrialized countries

Trends in Deaths from Selected Causes in Massachusetts

in the years two thousand
Antibiotics Classification: Site of action
Antibiotics Classification

Chemicals substances acting on bacteria

Inhibit the bacterial growth  Kill the bacteria

Bacteriostatic  Bactericidal
Antibiotics Classification: Chemical-physical characteristics

**Hydrophilic antibiotics**

- ✓ Beta-lactams
- ✓ Penicillins
- ✓ Cephalosporins
- ✓ Glycopeptidides
- ✓ Aminoglycosides

- ✓ Low distribution volume
- ✓ No cross cellular membranes
- ✓ No action on intracellular pathogens
- ✓ Renal elimination

**Lipophilic antibiotics**

- ✓ Macrolids
- ✓ Fluoroquinolones
- ✓ Tetracyclins
- ✓ Chloroamphenicol
- ✓ Rifampin

- ✓ High distribution volume
- ✓ Cross cellular membranes
- ✓ Action on intracellular pathogens
- ✓ Hepatic metabolism
Antibiotics Classification: activity

<table>
<thead>
<tr>
<th>Time-dependent</th>
<th>Concentration-dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Beta-lactams</td>
<td>• Aminoglycosides</td>
</tr>
<tr>
<td>• Glycopeptides</td>
<td>• Fluoroquinolones</td>
</tr>
<tr>
<td>• Tetracyclines</td>
<td>• Clarithromycin</td>
</tr>
<tr>
<td></td>
<td>• Azitromycin</td>
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</table>
The successful use of any therapeutic agent is compromised by the potential development of resistance to that compound from the time it is first employed.
The big problem of antibiotic resistance
Antibiotic Resistance: A Primer And Call To Action

During the golden age of discovery, 150 types of antibiotics were developed. Since then, the spread of resistance has greatly outpaced the rate of drug development. The Infectious Disease Society of America estimates that 70% of hospital-acquired infections in the United States are now resistant to one or more antibiotics.
Antibiotic resistance poses a serious and growing global problem

“This serious threat is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country. Antibiotic resistance—when bacteria change so antibiotics no longer work in people who need them to treat infections—is now a major threat to public health.”

Some pathogens have even become resistant to multiple type of classes of antibiotics
BAD BUGS: NO ESKAPE

- *Enterococcus*
- *S. aureus*
- *Klebsiella spp.*
- *Acinetobacter*
- *P. aeruginosa*
- *Enterobacter spp.*

# Antibiotic resistant infections

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Agents</th>
<th>Resistances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td><em>S. pneumoniae</em></td>
<td>Penicillin</td>
</tr>
<tr>
<td>Dysentery</td>
<td><em>S. dysenteriae</em></td>
<td>Multiple resistances</td>
</tr>
<tr>
<td>Typhoid</td>
<td><em>S. typhi</em></td>
<td>Multiple resistances</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td><em>N. gonorrhoeae</em></td>
<td>Penicillin and tetracycline</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td><em>M. tuberculosis</em></td>
<td>Rifampicine and INH</td>
</tr>
<tr>
<td><strong>Nosocomial infections</strong></td>
<td><em>S. aureus</em></td>
<td>Methicillin, vancomycin</td>
</tr>
<tr>
<td></td>
<td><em>E. species</em></td>
<td>Vancomycin</td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella, Pseudomonas</em></td>
<td>Multiple resistances</td>
</tr>
</tbody>
</table>
The increasing problem of antibiotic resistance has not been sufficiently contrasted.

<table>
<thead>
<tr>
<th>Urgent Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <em>Clostridium difficile</em></td>
</tr>
<tr>
<td>• Carbapenem-resistant Enterobacteriaceae (CRE)</td>
</tr>
<tr>
<td>• Drug-resistant <em>Neisseria gonorrhoeae</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serious Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Multidrug-resistant <em>Acinetobacter</em></td>
</tr>
<tr>
<td>• Drug-resistant <em>Campylobacter</em></td>
</tr>
<tr>
<td>• Fluconazole-resistant <em>Candida</em> (a fungus)</td>
</tr>
<tr>
<td>• Extended spectrum beta-lactamase-producing Enterobacteriaceae (ESBLs)</td>
</tr>
<tr>
<td>• Vancomycin-resistant Enterococci (VRE)</td>
</tr>
<tr>
<td>• Multidrug-resistant <em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td>• Drug-resistant nontyphoidal <em>Salmonella</em></td>
</tr>
<tr>
<td>• Drug-resistant <em>Salmonella Typhimurium</em></td>
</tr>
<tr>
<td>• Drug-resistant <em>Shigella</em></td>
</tr>
<tr>
<td>• Methicillin-resistant <em>Staphylococcus aureus</em> (MRSA)</td>
</tr>
<tr>
<td>• Drug-resistant <em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td>• Drug-resistant tuberculosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concerning Threats</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Vancomycin-resistant <em>Staphylococcus aureus</em> (VRSA)</td>
</tr>
<tr>
<td>• Erythromycin-resistant Group A <em>Streptococcus</em></td>
</tr>
<tr>
<td>• Clindamycin-resistant Group B <em>Streptococcus</em></td>
</tr>
</tbody>
</table>

Few molecules against antimicrobial resistance
Transmission of antibiotic resistance

In vertical transmission, a bacterium accumulates errors or mutations in its genome during replication; some of those changes give the ability to resist antibiotics and are passed on to subsequent generations.

In horizontal transmission, resistant genes are swapped from one microbe to another. Via transmission vectors (plasmid, phage etc)
Mechanisms of antibiotic resistance

Degradation of antibiotics

Overproduction of the target enzyme

Inactivation (add an phosphate group on the antibiotic, which will reduce its ability to bind to the bacterial ribosomes)

Modification (modified drug target)

Pumping out (increasing active efflux of the drugs)
Antibiotic Targets

- Cell Wall
  - β-lactams
  - Vancomycin
- DNA/RNA Synthesis
  - Fluoroquinolones
  - Rifamycins
- Folate Synthesis
  - Trimethoprim
  - Sulfonamides
- Cell Membrane
  - Daptomycin
- Protein Synthesis
  - Linezolid
  - Tetracyclines
  - Macrolides
  - Aminoglycosides

Antibiotic Resistance

- Efflux
  - Fluoroquinolones
  - Aminoglycosides
- Immunity & Bypass
  - Tetracyclines
  - Trimethoprim
  - Sulfonamides
  - Vancomycin
- Target Modification
  - Fluoroquinolones
  - Rifamycins
  - Vancomycin
  - Penicillins
  - Macrolides
  - Aminoglycosides

- Inactivating Enzymes
  - β-lactams
  - Aminoglycosides
  - Macrolides
  - Rifamycins
Beta-lactam antibiotics represent a large class of antibiotics. They can be grouped in first, second, third, and forth generation cephalosporins according to their spectrum of activity and timing of the agent’s introduction.
Mechanism of β-Lactam Action

- **Bactericidal**
- β-lactams bind and inhibit penicillin binding proteins (PBPs)
- PBPs are responsible for assembly, maintenance, and regulation of peptidoglycan (cell wall) metabolism.
- Disruption of peptidoglycan synthesis
Several mechanisms of antimicrobial resistance to $\beta$-lactam antibiotics

The most common mechanism through which bacteria can be come resistant is by expressing $\beta$-lactamases, which are grouped in a very large family.
Complexity of the interaction between the patient, pathogen and antibiotic

**Organism:** the bacteria phenotypes during antibiotic treatment

Time-kill curves of:

- ✔️ Susceptibility
- ✔️ Tolerance
- ✔️ Persistence

Susceptibility and resistance is measured by the minimum inhibitory concentration (MIC).

Tolerance is the capacity of a bacteria to stay alive in a fleeting exposure to antibiotics, which applies only to bactericidal antibiotics.

Persistence occurs in a bacterial subpopulation (classically <1%) that are not killed by antibiotics, and heterogeneous response is repeated when they are exposed to the same antibiotic.

*Front Pharmacol.* 2017;8:364.
Microbial persistence is on the road to drug resistance

## Persistence contributes to the pathogenesis of several notable human infections

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Duration of Treatment</th>
<th>Number of drugs</th>
<th>Persistence characteristics</th>
<th>Hosts susceptible to persistent infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mycobacteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>months</td>
<td>4</td>
<td>slow clearance</td>
<td>All, particularly HIV</td>
</tr>
<tr>
<td>Non-tuberculous <em>Mycobacteria</em></td>
<td>months-years</td>
<td>3–4</td>
<td>slow clearance, recurrence</td>
<td>All, particularly bronchiectasis, HIV</td>
</tr>
<tr>
<td><strong>Other bacteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>weeks–lifelong</td>
<td>1–2</td>
<td>biofilm, recurrence</td>
<td>Implanted material</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>days–weeks</td>
<td>1</td>
<td>biofilm</td>
<td>Urinary catheters</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>days–weeks</td>
<td>1–2</td>
<td>recurrence</td>
<td>CF, immunocompromized</td>
</tr>
<tr>
<td><em>Burkholderia pseudomallei</em></td>
<td>weeks</td>
<td>1–2</td>
<td>recurrence</td>
<td>All</td>
</tr>
<tr>
<td><em>Burkholderia cenocepacia</em></td>
<td>days - weeks</td>
<td>1–2</td>
<td>recurrence</td>
<td>CF</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida species</em></td>
<td>days–lifelong</td>
<td>1</td>
<td>slow clearance, recurrence</td>
<td>Cancer, immunocompromized, HIV</td>
</tr>
<tr>
<td><strong>Parasites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Plasmodium falciparum</em></td>
<td>days</td>
<td>1–2</td>
<td>recrudescence (artemisinins)</td>
<td>All</td>
</tr>
<tr>
<td><em>Babesia species</em></td>
<td>weeks months</td>
<td>1–2</td>
<td>recurrence</td>
<td>Immune-deficient</td>
</tr>
<tr>
<td><strong>Mammalian cells</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor cells</td>
<td>months</td>
<td>varies</td>
<td>recurrence</td>
<td>All</td>
</tr>
</tbody>
</table>

Environmental signals can modulate the level of persistence

- Intracellular stress
- Nutrient starvation
- Oxidative stress
- DNA damage
- Quorum sensing

Stress Response

Persistence

Adaptive Evolution

RESISTANCE

Patient: link between Pharmacodynamics and Pharmacokinetics

Pharmacokinetics:
- Absorption
- Distribution
- Elimination
- Antimicrobial dosing regimen

Pharmacodynamics:
- Time course concentration in serum
- Time course concentration at site of infection
- Pharmacologic and toxicologic effect
- Antimicrobial effect
The patient: changes in pharmacokinetics parameters

<table>
<thead>
<tr>
<th>Pathologic state</th>
<th>Physiologic change</th>
<th>Pharmacokinetic change</th>
<th>Drug classes affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical illness/ sepsis</td>
<td>↓ gastrointestinal perfusion, altered gastric</td>
<td>↓ oral absorption</td>
<td>all oral antibiotics</td>
</tr>
<tr>
<td></td>
<td>emptying</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ serum albumin</td>
<td>↓ protein binding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ fluid volume</td>
<td>↑ volume of distribution</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ renal perfusion</td>
<td>↓ renal clearance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ hepatic perfusion</td>
<td>↓ hepatic clearance</td>
<td></td>
</tr>
<tr>
<td>Burns</td>
<td>↑ renal perfusion</td>
<td>↑ renal clearance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ fluid volume</td>
<td>↑ volume of distribution</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>↑ total volume and adipose tissue</td>
<td>↑ volume of distribution</td>
<td></td>
</tr>
</tbody>
</table>

Table 2  Pharmacokinetic variation in pathophysiologic states
The patient: changes in pharmacokinetics parameters

<table>
<thead>
<tr>
<th>Considerations for dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased doses or i.v. antibiotics may be necessary if absorption cannot be assured.</strong></td>
</tr>
</tbody>
</table>
| Monitor for efficacy and drug interactions.  
  For highly protein-bound drugs, increase monitoring for adverse effects and drug-drug interactions.  
  Increased doses may be required to maintain optimal pharmacodynamic targets. |
| **Extended intervals and/or reduced doses may be required. Increase monitoring for clinical response and adverse effects.** |
| Dosage reduction may be advised, particularly in the setting of concurrent renal and hepatic dysfunction. |
| Maximum/increased doses or increased dosing frequency may be appropriate to maintain optimal pharmacodynamic targets. |
| Maximum/increased doses may be appropriate to maintain optimal pharmacodynamic targets. |
| Individualized weight-based dosing may be appropriate to maintain optimal pharmacodynamic parameters. |
Antibiotics are generally safe, but there are times when antibiotics can actually be harmful.

U.S. Department of Health and human Services
Many factors cause the antibiotic resistance

- Antibiotic Overuse: Although the number of antibiotic prescriptions varies by state, some states have more than one treatment per person per year.
- Inappropriate Prescribing: Approximately 30% of antibiotic prescriptions are incorrectly prescribed.
- Extensive Agricultural Use: Approximately 80% of antibiotics sold in the US are used as growth supplements for animals.
- Availability of Few New Antibiotics: Lack of funding and economic appeal for the pharmaceutical industry has led to a decrease in development of new antibiotics.
- Regulatory Barriers: Antibiotics are available over the counter and not regulated in some countries. In terms of new antibiotics development, regulatory obstacles pose a challenge.

Ventola C. The Antibiotic Resistance Crisis
Antimicrobial stewardship involves the *optimal drug selection, dose and duration* of an antibiotic resulting in the cure or prevention of infection with minimal unintended consequences to the patient including emergence of resistance, adverse drug events, and cost.
TAKE HOME A MESSAGE

“Appropriate use of antimicrobial agents involves obtaining an accurate diagnosis, determining the need for and timing of antimicrobial therapy, understanding how dosing affects the antimicrobial activities of different agents, tailoring treatment to host characteristics, using the narrowest spectrum and shortest duration of therapy, and switching to oral agents as soon as possible”.
To improve the use of today’s antibiotics, we must consider the factors influencing the DRUG SELECTION AND A CORRECT DRUG USE

Known Drug resistance

Pharmacodynamics

Pharmacokinetics

Patient’s characteristic

Therapeutic regimen
Thank you for your attention