The complex relationship between antibiotic prescription and resistance

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ESCMiD Postgraduate technical workshop
September 2015; Barcelona, Spain
Definition of resistance

- Two points of view to define resistance:
  - **Clinical**
    - Clinical S and R breakpoints are applied according to whether the in vitro inhibitory concentrations are associated with a high probability of success of antimicrobial therapy.
  - **Microbiological**
    - Presence of a resistance mechanism in a strain that reduces its susceptibility compared to that of the wild-type strain (ECOFF values).
    - The use of ECOFF values in assessing the impact of antibiotic use in resistance widens the spectra of resistance mechanisms analyzed.
Relationship between antibiotic consumption and resistance
Factors favoring the emergence of resistance

Facility to acquire resistance (fitness)
Inoculum
Persistence
Effect of resistance mechanism

Antibiotic use

Antibiotic Exposure
PK/PD parameters
Mutant selection window

Resistance
Facility to acquire resistance

- Resistant mutants are part of the normal susceptible population and emerge at a constant frequency. However, this frequency may vary depending on the antibiotic and the microorganism.
- Acquired resistance by gene mutation occurs spontaneously within a susceptible wild-type bacterial population at a very low frequency (<10^-9).
- **Hypermutator phenotype**: exhibit increased mutation frequency. Due to iterations in the methyl-directed mismatch repair system.
In hospitals with high antibiotic pressure antimicrobials can act as selective forces for bacterial evolution.
• MIC for bacteria with high inoculum are higher than those determined using classical tests
  – Reduction in the antibiotic concentration of high cell densities due to its binding to cell envelopes and debris of alive and killed cells
  – Existe of less molecules of antibiotic per cell at high inoculum

• Using experimental approaches and mathematical modeling, it has been shown that most likely both situations are relevant for inoculum-dependent antibiotic resistance. JAC (2009) 63: 745

• QS response might have a role in the inoculum-dependent antibiotics susceptibility of bacterial populations

• A high inoculum exceeding the inverse of mutational frequency substantially, there will be a high probability that multiple subpopulations of organisms will exist.
Persistence

- Quiescent intracellular bacteria
- In a bacterial population, there is a subpopulation of cells called *persisters* that are not killed by antibiotics in conditions that kill the bulk of the population
- Bacteria may survive for prolonged periods of time on inanimate surfaces, mainly associated with the production of *biofilm*
Biofilm: Congregation of bacterial cells irreversibly associated with a solid surface and enclosed within a polysaccharide matrix.

*In vitro* biofilm formation: liquid-air interface (ring structure)

Possible explanation for the resistance to desiccation and disinfection.
SURVIVAL IN THE ENVIRONMENT

Espinal P. (2012) JHI 80: 56-60
SURVIVAL IN THE ENVIRONMENT

- Studies of survival on dry surfaces
  - Biofilm-producing strains
    - 30 days
  - Non-biofilm-producing strains
    - 15 days

Liquid

Dry

BF (+)  BF (-)  BF (+)  BF (-)

BF (+)  BF (-)  BF (+)  BF (-)

Appendages

ESP layer

BF (-) Appendages

ESP layer
Effect of resistance mechanisms (Fitness)

- In some cases bacterial resistance produces a fitness cost and a decrease of virulence when measured "in vitro" or "in vivo".
- Antibiotic resistance also appears to enhance microbial fitness and virulence [Science Translational Medicine (2015) 7:297ra114]
- These so-called compensatory mutations may restore fitness.
Relationship between resistance and virulence in Acinetobacter spp. strains using the Caenorhabditis elegans model

Non-mammalian model whose innate immune system mimics that of the human being.
Clinical isolates highly resistant to colistin were less virulent than the counterparts.

Resistance to colistin in *A. baumannii* has been associated with lower *in vivo* bacterial fitness and decreased virulence.
The AdeABC efflux pump may represent a novel virulence factor for *Acinetobacter* spp. to resist innate immune defense.

Since efflux systems involve the extrusion of antimicrobial agents as well as other bacterial compounds, these compounds may have a role in virulence.
Factors favoring the emergence of resistance

- Facility to acquire resistance (fitness)
- Inoculum
- Persistence
- Effect of resistance mechanism

Antibiotic use

- Antibiotic Exposure
- PK/PD parameters
- Mutant selection window

Resistance
Antibiotic exposure

• Selection of resistant mutants (mutagenic power)
• Relationship between the concentration of the drug in the infection site and the MIC of the drug for the bacteria (MPC)
• Ratio between time of drug exposure and speed of bactericidal activity
The optimization of dosing regimens is accomplished by choosing the dose and schedule that will achieve the microbiological and clinical outcome desired and simultaneously will suppress emergence of resistance.

PK/PD of antimicrobial agents describe how the therapeutic drug effect is dependent on the potency of a drug against a microorganism and the exposure (the concentration of antimicrobial available for effect over time).
For some antibiotics (e.g., aminoglycosides) the activity is known to be highly dependent on the maximum concentration reached, while for others (e.g., b-lactams) it is more dependent on the exposure time.

Three PK/PD parameters to predict antimicrobial efficacy:

- Peak concentration divided by MIC (Cmax/MIC)
- Time above the MIC (t > MIC)
- Area under the 24-h concentration-time curve above MIC (AUC/MIC)
Mutant selection window (MSW)

**MPC**, which is above the MIC, is defined as the concentration that restricts the emergence of first-step resistant mutants within a susceptible population.
Measures to avoid the emergence of resistance

Restriction of antimicrobials

Cycling vs mixing therapy

Use of combination therapy

Antibiotic use

Resistance

Antimicrobial stewardship
Restriction of antibiotics

- Reducing the rate of use of antibiotics for which there is resistance
- Increasing the rate of use of a drug for which there is no resistance
- Reducing the overall rate of transmission of bacteria in hospitals
- Increasing the rate turnover (reducing term of stay)

Minimizing potential resistance: A population dynamics view
Cycling versus mixing

• Typical cycling protocols use periods of one to several months. The theoretical benefit of cycling primarily is based on the assumption that resistance affects only single antibiotics or antibiotic classes and that resistant bacteria are less fit and will have a growth disadvantage upon withdrawal of the selective antibiotic pressure. Resistance should then decrease during periods of non-exposure, which would justify cycling protocols.

• The main drawback in implementing this strategy is the high prevalence of multidrug resistant bacteria in nosocomial setting
To investigate the risk factors for the acquisition of *P. aeruginosa* and its resistance phenotypes in critically-ill medical patients taking into account colonization pressure and antimicrobial exposure variables.
• **Design:** Prospective cohort study.
• **Setting:** An 8-bed medical intensive care unit in a 700-bed university hospital.
• **Patients:** 850 patients admitted for at least three days during a 35-month period.
• **Interventions:** Nasopharyngeal and rectal swabs and respiratory secretions were obtained and cultured within 48 hours of admission and thrice weekly thereafter. During the study, a policy of consecutive mixing-cycling periods of three classes of antipseudomonal agents (meropenem, ceftriaxone/piperacillin-tazobactam, ciprofloxacin/levofloxacin) was implemented in the unit. Outcome variables were the acquisition of *P. aeruginosa* and of its different resistance phenotypes. Multivariate models were constructed by logistic regression analysis.
105 (12%) patients acquired at least one strain of *P. aeruginosa*. Multivariate analysis selected admission due to primary bacteremia (OR 18.2; 4.9-66.9), emergency surgery (OR 2.5; 1.4-4.6), intubation (OR 2.8; 1.3-5.9 for ≤3 days, and OR 4.2; 1.9-9.2 for >3 days), enteral nutrition for ≤3 days (OR 3.9; 1.8-8.1), parenteral nutrition for ≤3 days (OR 3.5; 1.4-8.6), tracheostomy (OR 4.4; 2.3-8.6) and colonization pressure >0.43 (OR 3.8; 1.2-12.1) as independently associated with the acquisition of *P. aeruginosa*, while being colonized by *P. aeruginosa* on admission (OR 0.03; 0.01-0.2) and exposure to fluoroquinolones for >3 days (OR 0.5; 0.3-0.9) were protective.
CONCLUSIONS

- Colonization pressure being defined as the proportion of patients colonized with a particular organism in a defined geographic area within a hospital during a specified time period.
  - In the ICU setting, colonization pressure may be more important than antibiotic exposure as a determinant of P. aeruginosa acquisition.
  - Fluoroquinolones may decrease the acquisition burden of this pathogen in previously non-colonized patients.
  - Antipseudomonal carbapenems are the antibiotics most clearly associated with the acquisition of resistance to themselves and multiple drugs.
The use of combinations of antimicrobial agents is a common practice during clinical therapy, most notably for the treatment of severe infections and empirical therapy. Combination therapy in some instances may prevent the emergence of resistance. Use combination therapy for severely ill patients. Use combination therapy for specific indications (e.g., Pseudomonas infections).
Antimicrobial stewardship

- Education
- Formulary restriction and pre-authorization
- Antimicrobial order forms
- Guidelines and clinical pathways
- Streamlining or de-escalation of therapy
- Parenteral to oral conversion
Urinary tract infections (UTIs) in men: Collected urinary samples from 560 male patients (>18 years) suspected of UTI and recorded prescribed antibiotic treatment

A significantly higher proportion of female UTIs was caused by *E. coli* compared with men (72% versus 51%, *P*=0.05). *E. coli* susceptibility tended to be lower in men compared with women, although not reaching statistical significance. No changes in *E. coli* susceptibility were observed over time (< *P*<0.05).

Empirical male UTI treatment options should be based on surveillance studies including men only.
Among 9,798 consecutive, non-duplicate, community-source urine isolates from ambulatory patients ≥ 13 years old, from clinical laboratory and an academic medical center in Curitiba, Brazil.

- Males exhibit low susceptibility rates than females.
- Within each gender susceptibility declined with increased age.

Ratio female/male

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Male</th>
<th>Female</th>
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<td>13-20</td>
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<td>3.3</td>
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<td>32-40</td>
<td>3.3</td>
<td>28.1</td>
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<td>41-50</td>
<td>3.3</td>
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<tr>
<td>&gt; 80</td>
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<td>28.1</td>
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Compartments of selection

Non hospital compartment:
- Community patients, food and wild animals and environment
  - Antimicrobial resistance genes
  - Resistant bacteria
  - Antimicrobial use in the community patients and in food animals
  - Antimicrobials in the environment

Hospital compartment:
- Antimicrobial resistance genes
- Resistant bacteria
- Antimicrobial use in the hospitals