Infectious Disease Controversies
Bacteria and Neutropenia
8.45-9.30
How to manage infections caused by antibiotic resistant Gram-negative bacteria

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Infectious Disease Controversies
How to manage infections caused by antibiotic resistant Gram-negative bacteria

- Epidemiology
- Clinical impact
- Management
  - Pharmacological treatment
    - Empirical
    - Targeted
  - Prevention
    - Limit inducing new resistance
    - Infection control measures
- Antimicrobial stewardship
Aetiology of BSI
38 leukemia centers

2011 ECIL-4 Surveillance study

- S. aureus, 5% (0-15%)
- CNS, 24% (7-51%)
- Viridans streptococci, 6% (0-22%)
- Enterococci, 8% (0-30%)
- Other Gram+, 5% (0-15%)
- Enterobacteriaceae, 30% (8-56%)
- P. aeruginosa, 5% (0-28%)
- Acinetobacter, 2% (0-11%)
- Other Gram-, 3% (0-14%)
**KPC Kp – clinical impact**

- **Mortality in case of bacteremia:** 22%-72%
- Colonizzazion can last months
- 10-30% of colonised patients will develop and infection

Qureshi CMI 2012; Hirsch JAC 2012; Tumbarello CID 2012; Borer Infec Control Epidem 2009;
### Blood cultures May 2011: *K. pneumoniae*

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>&gt;64</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;4</td>
<td>R</td>
</tr>
<tr>
<td>Amox/clav</td>
<td>&gt;32</td>
<td>R</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;16</td>
<td>R</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>&gt;64</td>
<td>R</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>&gt;64</td>
<td>R</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>&gt;64</td>
<td>R</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>&gt;16</td>
<td>R</td>
</tr>
<tr>
<td>Imipenem</td>
<td>&gt;16</td>
<td>R</td>
</tr>
<tr>
<td>Meropenem</td>
<td>&gt;16</td>
<td>R</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>&gt;128</td>
<td>R</td>
</tr>
<tr>
<td>Pip/taz</td>
<td>&gt;128</td>
<td>R</td>
</tr>
<tr>
<td>Colistin</td>
<td>&gt;16</td>
<td>R</td>
</tr>
</tbody>
</table>

### Risk factors for MDR infection
- The influence that MDR infection has on the treatment of the underlying condition (HSCT or not)
- Choice of empirical therapy
- Risk of an outbreak, the importance of contact precautions
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Empirical treatment of febrile neutropenia in patients at risk of infections due to resistant Gram-negatives

- Target immediately the most dangerous and the most probable suspect
- Standard choice, such as ceftazidime, cefepime, piperacillin/tazobactam, carbapenem might not be sufficient if a patient is infected with a resistant Gram-
How to find the right balance?

- Growing resistance to standard antibiotics leads to increased use of broad-spectrum regimens, including carbapenems and combinations.
- Consequent collateral damage, including the selection of carbapenem- and multidrug resistant (MDR) pathogens, predisposition to fungal infections and *Clostridium difficile*-associated diarrhea.
- Patients with infections due to resistant pathogens:
  - ESBL+ or AmpC-β-lactamase-producing Enterobacteriaceae
  - MDR *P. aeruginosa*,
  - MDR *Acinetobacter* spp.
  - *Stenotrophomonas* spp.
- Are significantly more likely to receive an inadequate empirical antibiotic therapy.
- The time to appropriate therapy is much longer.
- Inappropriate initial therapy predicts increased mortality.

Who is at risk for infection with resistant bacteria?

- Prior infection
- Prior colonization
- Centers with high prevalence of resistant bacteria
- Adequate past medical history, including susceptibility testing results
- Surveillance swabs
- Knowledge of local epidemiology
New approach to empirical therapy of febrile neutropenia

Escalation strategy

- Covers **typical** Enterobacteriaceae and *P. aeruginosa*, but not ESBL, KPC, MDR
- If the patient deteriorates, or a resistant pathogen is isolated, therapy is escalated

  - **Pro**: Avoids early use of combination therapy or broadest-spectrum antibacterials, including carbapenems
  - **Less toxicity and cost**
  - **Less selection of carbapenem resistance**

- **Con**: If initial empirical therapy fails to cover the pathogens in neutropenic patients, prognosis is significantly worsened

De-escalation

- Initial coverage of MDR, *e.g.* carabapenem + anti-MRSA agent/aminoglycosides
- Therapy is de-escalated to a simpler or narrower spectrum (‘targeted’) therapy once resistant pathogens are **NOT** isolated

  - **Pro**: More likely to achieve cover in the first 48h, before microbiology data available
  - **Con**: Leads to unnecessary use of broad-spectrum antibiotics in many patients
  - **Common failure to de-escalate when possible to do so**
  - **Consequent risk of selecting for resistance (especially for carbapenems)**
ECIL Indications for De-escalation Strategy \textit{BII}

De-escalation should be applied for patients with

- \textit{Known colonisation with resistant bacteria}
- \textit{Previous infections with resistant bacteria}
- \textit{In centres where resistant pathogens are regularly seen at the onset of febrile neutropenia}
- \textit{Complicated presentations}

\textit{Antimicrobial stewardship}

\textit{Averbuch D. et al. Haematologica 2013: 98 (12)}
Antibiotics

Escalation strategy

- Anti-pseudomonal cephalosporin (cefepime, ceftazidime)
- Piperacillin/tazobactam

De-escalation

- Carbapenem
- Combination of anti-pseudomonal β-lactam (carbapenem) and aminoglycoside (or FQ)
- Anti-pseudomonal β-lactam + coverage of resistant-Gram-positives (a glycopeptide or newer agent)
- Colistin + β-lactam ± rifampicin
- Any other combination based on colonisation/prior infection data
Antimicrobial stewardship
Duration of Empirical Therapy in Neutropenic Patients

• Relapse of fever and bacterial infection are independent of discontinuing antibiotic therapy during neutropenia or after its resolution
• With appropriate antibiotic therapy, FUO has low mortality, unless patient is in septic shock
• Discontinue iv empirical antibacterials after ≥ 72h
  - If patient has been afebrile ≥ 48h and is stable
  - Irrespective of neutrophil count or expected duration of neutropenia

BII

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Antimicrobial stewardship
## Therapeutic options for MDR

<table>
<thead>
<tr>
<th>Drug, year of approval</th>
<th>MRSA</th>
<th>VRE</th>
<th><em>P. aeruginosa</em> MDR</th>
<th><em>K. pneumoniae</em> MDR</th>
<th><em>A. baumannii</em> MDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid 2000</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Daptomycin 2003</td>
<td>+</td>
<td>+?</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tigecyclin 2005</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-/+</td>
<td>+</td>
</tr>
<tr>
<td>Doripenem 2007</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ceftobiprole 2008 *</td>
<td>+</td>
<td>-/+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Telavancin 2009</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ceftarolin 2010</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fosfomycin 1969**</td>
<td>-</td>
<td>-</td>
<td>-/+</td>
<td>-/+</td>
<td>-/+</td>
</tr>
<tr>
<td>Colistin 1956</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* Active against *E. faecalis* not *E. faecium*; * Year of discovery

**
# Targeted treatment

<table>
<thead>
<tr>
<th>Resistant bacteria</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbapenem-resistant Enterobacteriaceae</strong></td>
<td>- Colistin/polymyxin B* BII</td>
</tr>
<tr>
<td></td>
<td>- Tigecycline* BIII</td>
</tr>
<tr>
<td></td>
<td>- Aminoglycosides* BIII</td>
</tr>
<tr>
<td></td>
<td>- Fosfomycin* CIII</td>
</tr>
<tr>
<td><strong>Beta-lactam-resistant</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
<td>- Colistin/polymyxin B* All</td>
</tr>
<tr>
<td></td>
<td>- Fosfomycin* CIII</td>
</tr>
<tr>
<td><strong>Beta-lactam-resistant</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Acinetobacter spp.</strong></td>
<td>- Colistin/polymyxin B* BIII</td>
</tr>
<tr>
<td></td>
<td>- Tigecycline* BIII</td>
</tr>
<tr>
<td><strong>Stenotrophomonas maltophilia</strong></td>
<td>- Trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>(TMP-SMX) Al</td>
<td>- Fluoroquinolone (ciprofloxacin or moxifloxacin) BII</td>
</tr>
<tr>
<td></td>
<td>- Ticarcillin-clavulanate BII</td>
</tr>
<tr>
<td></td>
<td>In seriously-ill or neutropenic patients, combination therapy can be considered (e.g. TMP-SMX + ceftazidime or ticarcillin-clavulanate) CIII</td>
</tr>
<tr>
<td><strong>Vancomycin-resistant</strong></td>
<td>- Linezolid All</td>
</tr>
</tbody>
</table>

Treatment of MDR Gram-Which combination?

Colistin + tigecyclin
Colistin + gentamycin
Gentamycin + tigecyclin
Colistin + tigecyclin + high dose carbapenems
Double carbapenem (ertapenem + doripenem?) +
Gentamycin +
Colistin + rifampin?
Fosfomicin? +

<table>
<thead>
<tr>
<th>Variables</th>
<th>P value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation with septic shock</td>
<td>0.008</td>
<td>7.17 (1.65-31.03)</td>
</tr>
<tr>
<td>Inadequate initial antimicrobial treatment</td>
<td>0.003</td>
<td>4.17 (1.61-10.76)</td>
</tr>
<tr>
<td>High APACHE III score</td>
<td>&lt;0.001</td>
<td>1.04 (1.02-1.07)</td>
</tr>
<tr>
<td>Post-antibiogram therapy with tigecycline + colistin + meropenem</td>
<td>0.01</td>
<td>0.11 (0.02-0.69)</td>
</tr>
</tbody>
</table>

Tumbarello CID 2012; Petrosillo Inv Drug Rev 2012
Optimal use of antibiotics
PK/PD

- Correct drug and dose for the given indication and MIC and BMI
  - Sepsis – high serum levels, bactericidal, not bacteriostatic, if available (beta-lactams better than tigecyclin)
  - Cholangitis – agents with biliary excretion (penicillins not cephalosporins)
  - UTI - agents with urinary excretion (beta-lactams, AG, FQ, not tigecyclin)
  - Pneumonia – those distributed well to lung epithelium and active there (daptomycin is inhibited by surfactant)

- Meropenem 3-6g/daily
- Colistin? Probably 9,000,000 IU/day
- Fosfomycin? 16-24g/day
Optimal use of antibiotics
PK/PD

- Correct administration schedule
  - Rapid once daily administration for concentration-dependent molecules (aminoglycosides, daptomycin, FQ)
  - Continuous/prolonged infusion for time-dependent drugs such as beta-lactams
  - Loading dose in order to achieve more rapidly the effective concentration, particularly if a continuous infusion is used
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Infection control measures

1. hand hygiene (including alcohol based hand disinfection)
2. antiseptic whole body washing (daily bathing with chlorexidine gluconate impregnated washcloths) against MRSA
3. appropriate environmental cleaning
4. screening for carriage, and, in case of a positive result,

CONTACT PRECAUTIONS
- patient's isolation or cohorting
- staff cohorting
- appropriate environmental cleaning
- (decolonization ?)

ECIL initial (at admission) and regular screening, once or twice weekly, for GI colonization with resistant bacteria should be considered in centers with a high prevalence of resistance

MRSA, VRE, ESBL, KPC, …?

The principles of antimicrobial stewardship

Multidisciplinary: treating physicians, ID specialist, microbiology lab, pharmacy, hospital authorities

Aim: improve the outcome of infections + limit the spread of resistance

1. Local surveillance of antibiotic resistance, consumption and patient outcomes, with regular monitoring reports (every 6 months), alerts
2. Development and regular update of protocols and algorithms for the diagnosis, prevention and treatment of infections
3. Swift reporting of microbiological results by the laboratory, allowing timely de-escalation of broad-spectrum empirical regimens and shortening of antibiotic therapy
4. Optimization of dosing regimens based upon PK/PD principles, particularly for high-risk patients
5. Frequent multidisciplinary grand rounds

Management of resistant Gram- in HSCT

Take home messages

1. MDR bacteria are increasingly frequent in HSCT recipients, but significant differences in their prevalence exist between centers.
2. Local data should be collected and should guide management policies.
3. Empirical therapy should be individualized, and an escalation or de-escalation approach should be chosen depending on local epidemiology, colonization and clinical presentation.
4. Combination therapy is warranted for most infections due to MDR Gram-negatives.
5. Infection control measures are mandatory to limit the spread of resistant strains.
6. Antimicrobial stewardship should be in place in all transplant units.