Infections in haematological patients

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Disease
BMT
Chemotherapy

IV devices
Neutropenia
Immunodefficiency

Infections
Bacterial
Fungal
Viral
Protozoal
Distribution of episodes of bloodstream infection (BSI) and pneumonia among 18 hospitals participating in the study.

Burden of Bacterial Infections

BMT 834 patients

BSI within 100 days
349 (42%) patients

613 episodes
88% G-pos
7% G neg

Biol Blood Marrow Transplant. 2012 (in press)
Distribution of pathogens in patients with HCA infections after BMT

Etiology of BSI

- Autologous transplant recipients
  - CNS (n=50),
  - *Enterococcus* species (n=5)
  - *Corynebacterium* nos (n=4).

- Allogeneic transplant recipients
  - CNS (n=34)
  - *Enterococcus* species (n=151)
  - *Pseudomonas* species (n=28)

Biol Blood Marrow Transplant. 2012 (in press)
Therapeutic problems of bacterial infections

- **Gram-positives**
  - Increasing vancomycin MIC
  - VRE
    - Linezolid
    - Daptomycin
    - Ceftaroline
    - Etc.
  - Etc.

- **Gram negatives**
  - MDR P. aeruginosa
    - panresistant
  - MDR Acinetobacter
    - Colistin
    - Amp/Sulbactam
    - Colistin+imipenem
    - Colistin + tygecycline
  - ESBL K. pneumoniae
    - Penems
  - KPC
    - colistin
The outcome of MR infections depends on the appropriate antibiotic choice.

Factors in choosing an antibiotic regimen

Local bacterial epidemiology and resistance patterns

Patient’s prior colonization or infection by resistant pathogens, particularly:

- MRSA and MRSE, especially with vancomycin MICs > 2 mg/L
- Vancomycin-resistant enterococci
- ESBL- or carbapenemase-producing Enterobacteriaceae
- A. baumannii, Pseudomonas spp. & S. maltophilia

Other patient-related factors

- Other risk factors for infection due to resistant pathogens
- Clinical presentation
Therapeutic strategy in FNP and high risk patients for infection with MDR bacteria

- **Gram-negative coverage**
  - Antipseudomonal antibiotics
    - Imipenem
    - Cefepime, Ceftazidime
    - Piperacillin-tazobactam
  - + anti MRSA antibiotics
    - Vancomycin
    - Teicoplanin
    - Linezolid
    - Daptomycin etc.

- **Deescalation**

Cefepime and Pip/Taz are not active against ESBL+
De-escalation approach

• Pro: More likely to achieve cover in the first 48h, before microbiology data become 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)
Early appropriate therapy for MR bugs
Empiric broad-spectrum antibiotic therapy of nosocomial pneumonia in the intensive care unit: a prospective observational study

- Overall de-escalation rate: 23% (56/244 pts)

The incidence of de-escalation

<table>
<thead>
<tr>
<th>%DE-ESC.</th>
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<tbody>
<tr>
<td>1</td>
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<td>2</td>
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<td>3</td>
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<td>5</td>
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<tr>
<td>6</td>
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</table>

- ICAAC 2010, 2011
- >50%
- De-escalation was 100% (21 of 21) in the intensive care unit (ICU) and 75% (54 of 72) on the medical-surgical floors ($p = 0.01$).
  - **R. J. Eastin** K-1876, 50th ICAAC Boston, 2010
- **DE has shown to be an effective strategy to reduce selective pressure and the incidence of multi-drug resistant organisms.** Ertapenem (ETP) may play a role in DE, reducing the unnecessary *Pseudomonas aeruginosa* coverage once the culture reports a MDRE, but evidence of its use in the ICU is lacking.
- **J. J. Maya – Researcher, K-1468, 51st ICAAC, 2011**

1. Alvarez-Lerma CC 2006
2. Rello J CCM 2004
3. Eachempaty J Trauma 2009
4. Morel J CC 2010
5. De Waelle JCC 2010
ECIL Guidelines for Empirical Treatment of Febrile Neutropenia De-escalation Strategy De-escalation should be applied for patients

—With complicated presentations

—With individual risk factors for resistant pathogens,

—In centres where resistant pathogens are regularly seen at the onset of febrile neutropenia BII

• Review of infection control is mandatory
Suggested initial regimens in a de-escalation strategy

• Carbapenem monotherapy

• Combination of anti-pseudomonal β-lactam + aminoglycoside or quinolone
  
  – *With carbapenem as the β-lactam in seriously ill-patients*

• Colistin + β-lactam or rifampicin etc.

• Early coverage of resistant-Gram +ves with a glycopeptide or newer agent
First-line carbapenems should be reserved for situations where:

• Known colonization or previous infection with:
  
  – ESBL-producing Enterobacteriaceae

  – Gram -ves resistant to narrower-spectrum b-lactams BII

• Seriously-ill patients

  – e.g. presentation with septic shock, pneumonia BII

• Centres with a high prevalence of infections due to ESBL-producers at the onset of febrile neutropenia

  – Should also prompt infection control review BIII
Initial empirical therapy for febrile, high-risk patients with uncomplicated neutropenia

- Anti-pseudomonal ceph (cefepime*, ceftazidime*) AI

- Piperacillin-tazobactam AI

- Other possible options include:
  - Anti-pseudomonal carbapenem** AI
  - Ticarcillin-clavulanate, cefoperazone-sulbactam

* Avoid if ESBLs are prevalent
** AI for efficacy, but should be avoided in uncomplicated patients lacking risk factors for resistant bacteria, to preserve activity for seriously-ill patients

ECIL 4, 2011
Initial therapy in patients colonised or previously infected by resistant Enterobacteriaceae

<table>
<thead>
<tr>
<th>Resistance type</th>
<th>Treatment</th>
</tr>
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</table>
| ESBL            | Carbapenem*  
Carbapenemase  
Colistin* CIII  
+/- one of: Tigecycline* CIII or Aminoglycoside CIII or Fosfomycin CIII |
|                 | * BII     |
|                 | CIII     |
Mortality in ESBL vs. non-ESBL Enterobacteriaceae bacteraemia
Delay in appropriate $R_x$ ESBL vs. non-ESBL Enteric bacteraemia

First author

Schwaber
Tumbarello
Marra
Endimiani
Kang
Kim BN
Du
Ho
Menashe
Pena
Pooled

Relative risk

0.91

5.56

Schwaber & Carmeli JAC 2007 60:913
Haematology patients with ESBL producers more often receive inappropriate initial antibiotics

<table>
<thead>
<tr>
<th>Study</th>
<th>% treatments inappropriate</th>
<th>No of episodes; causative bacteria; ESBL rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESBL +ve</td>
<td>ESBL -ve</td>
</tr>
<tr>
<td>Gudiol et al.</td>
<td>65%</td>
<td>6%</td>
</tr>
<tr>
<td><em>J Antimicrob Chemother 2010</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ortega et al.</td>
<td>52%</td>
<td>5%</td>
</tr>
<tr>
<td><em>J Antimicrob Chemother 2009</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumbarello et al.</td>
<td>50%</td>
<td>2%</td>
</tr>
<tr>
<td><em>Antimicrob Agents Chemother 2006</em></td>
<td></td>
<td></td>
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</tbody>
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ECIL 4 - [Bacterial Resistance in Haematology](#) - 2011
Kang et al. AAC 2004

Survival probability

Days after bacteremia

- Carbapenem
- Ciprofloxacin
- Others
Imipenem vs. ertapenem u liječenju ESBL+ infekcija (73 ertapenem, 171 imip/mero)

A

![Graph A]

Pitt bacteremia score <4
P = 0.57

B

![Graph B]

Pitt bacteremia score >= 4
P = 0.52

Diagn Microbiol Infect Dis.
2011;70:150-3.
Ertapenem vs. other penems in patients with ESBL+ BSI

- 261 patients
- Hospital mortality

### Ertapenem: impact on resistance after 7 months of use

<table>
<thead>
<tr>
<th>Isolate (No of isolates in two periods)</th>
<th>Imipenem</th>
<th>Amp/Sulb</th>
<th>Pip/Tazo</th>
<th>Cefepime</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>K. pneumoniae</em> - ESBL (22/40)</td>
<td>95/100</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td><em>E. coli</em> (979/1026)</td>
<td>100/100</td>
<td>77/72*</td>
<td>96/93*</td>
<td>100/100</td>
</tr>
<tr>
<td><em>E. coli</em> - ESBL (0/11)</td>
<td>NT/100</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td><em>E. cloacae</em> (191/211)</td>
<td>100/98</td>
<td>NT</td>
<td>79/76</td>
<td>89/89</td>
</tr>
<tr>
<td><em>S. marcescens</em> (138/115)</td>
<td>90/98*</td>
<td>NT</td>
<td>79/92*</td>
<td>93/98</td>
</tr>
<tr>
<td><em>P. aeruginosa</em> (785/741)</td>
<td>71/71</td>
<td>NT</td>
<td>82/89*</td>
<td>72/76</td>
</tr>
</tbody>
</table>

Goff DA, Mangino J. ICAAC 2004, Abstract K-343

*p<0.05*
Carbapenem utilization and *P. aeruginosa* susceptibilities to imipenem

Goff DA & Mangino JE. J Infection 2008
Conclusion

• “Selective concentration pertains only very briefly \textit{in vivo}, militating against selection in the patient”—Livermore DM et al

• Like ceftriaxone which does not favor the selection of imipenem-resistant \textit{P. aeruginosa}

Hospital Use of Ertapenem and its Impact on Carbapenem-resistance in *Acinetobacter* spp. and *Pseudomonas* spp. Infections

- **Acinetobacter** (1,525 strains)
  - meropenem-resistance OR 1.22; CI 95% 1.06-1.40
  - imipenem-resistance OR 1.13; CI 95% 0.99-1.28

- **Pseudomonas** (5,616 strains)
  - meropenem resistance OR 0.96; CI 95% 0.93-1.00
  - imipenem resistance OR 1.01; CI 95% 0.98-1.04

- Reduction in the frequency of *Acinetobacter* spp. (OR 0.94; CI 95%, 0.90-0.96) and *Pseudomonas* spp. (OR 0.97; CI 95% 0.95-0.98) infections.

A. C. PASQUALOTTO, ICAAC 2010, K-246
Resistance to ertapenem

- Taiwan
- 251 patients with bacteremia caused by ESBL-producing Escherichia coli and Klebsiella pneumoniae treated by a carbapenem

Lee NY. AAC 2012; 56:2888-93
Bacterial infections in haematological patients

- Never ending story (vicious cycle)
- New antibiotics for gram-negatives are lacking
- Prudent use of existing antibiotics is mandatory