Empirical Treatment Strategies of
the Immunocompromised Host
in the Era of MDR Organisms

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Single Agent Bacteremia in EORTC-IATG Trials

* These studies predominantly included patients with low-risk neutropenia

Adapted from Viscoli C. Eur J Cancer 2002;38(suppl 4):S82
ESKAPE Pathogens

- Enterococcus faecium
- Staphylococcus aureus
- Klebsiella pneumoniae
- Acinetobacter baumannii
- Pseudomonas aeruginosa
- Enterobacter spp.

Rice LB. *J Infect Dis.* 2008;197:1079
Rice LB. *Infect Control Hosp Epidemiol.* 2010;31(Suppl 1):S7
Introduction to ECIL

from ECIL1 to ECIL 4

4th European Conference on Infections in Leukemia
Current Epidemiology of Bacteremia in Cancer Patients

- 34 centers from Europe and Israel
- Median observation period, 4 years (range 1-13)
- 21 adult-only, 6 children-only centers
- Gram (+) vs (-) pathogens, 56% vs 44%
- Resistance rates for Gram (-)s higher in south/east vs north/west countries

Current Epidemiology of Bacteremia in Cancer Patients, ECIL 4

<table>
<thead>
<tr>
<th>Bacterial Group</th>
<th>Median Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>7-21%</td>
</tr>
<tr>
<td>Enterococci</td>
<td>0-30%</td>
</tr>
<tr>
<td>Viridans strep.</td>
<td>0-22%</td>
</tr>
<tr>
<td>S. aureus</td>
<td>0-15%</td>
</tr>
<tr>
<td>Other Gram (+)</td>
<td>0-15%</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>8-56%</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>0-28%</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>0-11%</td>
</tr>
<tr>
<td>Other Gram (-)</td>
<td>0-14%</td>
</tr>
</tbody>
</table>

Current Resistance Rates, ECIL 4

Median intervals (with range)

ESKAPE Pathogens in Cancer Patients

- Bacteremia in adult cancer patients, 2006-2011
  - 1148 bacteremia episodes
    - 392 (34%) ESKAPE pathogens
      - 54 (4.7%) rESKAPE
      - VRE
      - MRSA
      - ESBL (+) K. pneumonia
      - Carba-R A. baumannii
      - Carba- and Q-R P. aeruginosa
      - Derepressed and ESBL (+) Enterobacter spp.

rESKAPE Bacteremia (n=54)
Risk Factors

<table>
<thead>
<tr>
<th>Risk factors vs ESKAPE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidities</td>
<td>.02</td>
</tr>
<tr>
<td>Prior antibiotics (1 mo)</td>
<td>.001</td>
</tr>
<tr>
<td>Urinary catheter</td>
<td>.02</td>
</tr>
<tr>
<td>Urinary tract source</td>
<td>.04</td>
</tr>
</tbody>
</table>

vs matched controls w/o bacteremia (n=54)

| Prior antibiotics (1 mo)                    | <.001   |
| Urinary catheter                            | .05     |
### rESKAPE Bacteremia (n=54)
Risk Factors for Case Fatality Rate (30 days)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Persistent sepsis</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Steroid therapy</td>
<td>.007</td>
</tr>
<tr>
<td>Empirical, beta-lactam mono-therapy</td>
<td>.001</td>
</tr>
<tr>
<td><strong>Protective factors</strong></td>
<td></td>
</tr>
<tr>
<td>Infection recovery</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Empirical, beta-lactam + aminoglycoside therapy</td>
<td>.03</td>
</tr>
</tbody>
</table>

Agents of Bacteremia in Cancer Patients

Guven GS, et al. Support Care Cancer 2006;14:52
Distribution of Agents of Gram (-) Bacteremia

* 47.5% were Acinetobacter spp.

Guven GS, et al. Support Care Cancer 2006;14:52
Resistance Patterns in *E. coli* and *Klebsiella* spp. in Cancer Patients

Resistance Patterns in *P. aeruginosa* and *Acinetobacter* spp. in Cancer Patients

Quinolone-R *E. coli* in Neutropenic Cancer Patients with Levofloxacin Prophylaxis

- 207 neutropenia episodes (142 pts)
- All received levo prophylaxis, 500 mg bid

- 93 (44.9%) QR-EC colonization at admission
- 9 (9.7%) QR-EC bacteremia
- 48 (42.1%) Colonization disappeared during LP

- 114 (55.1%) No colonization at admission
- 48 (42.1%) Colonized during LP
- 6 (12.5%) QR-EC bacteremia
- 66 (57.9%) No colonization
- No QR-EC bacteremia

Other Results and Conclusions

• 40% QR-EC were ESBL producers
  – Only carbapenems and amikacin effective in vitro
• Colonizing and bacteremia strains shared the same PFGE patterns
• Carbapenems should be the empirical choice for patients under levo prophylaxis

Etgül S, et al. ICAAC 2014 Abst no. C-1433
Proportion of Carbapenems Resistant (R+I) *Klebsiella pneumoniae* Isolates in Participating Countries in 2013

Percentage resistance:
- < 1%
- 1 to < 5%
- 5 to < 10%
- 10 to < 25%
- 25 to < 50%
- ≥ 50%
- No data reported or less than 10 isolates
- Not included

(C) ECDC/Dundas/TESSy
Multidrug-resistant Klebsiella pneumoniae Isolates in Participating Countries in 2013 (Resistant to Third-generation Cephalosporins, Fluoroquinolones and Aminoglycosides)

Percentage resistance:
- < 1%
- 1 to < 5%
- 5 to < 10%
- 10 to < 25%
- 25 to < 50%
- ≥ 50%
- No data reported or less than 10 isolates
- Not included

(C) ECDC/Dundas/TESSy
Consecutive non-replicate clinical isolates (n=191) of carbapenem non-susceptible Enterobacteriaceae were collected from 21 hospital laboratories across Italy from November 2013 to April 2014 as part of the European Survey on Carbapenemase-producing Enterobacteriaceae (EuSCAPE) project. Klebsiella pneumoniae carbapenemase-producing K. pneumoniae (KPC-KP) represented 178 (93%) isolates with 76 (43%) respectively resistant to colistin, a key drug for treating carbapenemase-producing Enterobacteriaceae. KPC-KP colistin-resistant isolates were detected in all participating laboratories. This underscores a concerning evolution of colistin resistance in a setting of high KPC-KP endemicity.

We report the widespread and rapid dissemination of resistance against colistin, a key drug for treatment of carbapenemase-producing Enterobacteriaceae, among Klebsiella pneumoniae carbapenemase (KPC)-producing K. pneumoniae (KPC-KP) in Italy. As part of the European Survey on Carbapenemase-producing Enterobacteriaceae (EuSCAPE) project, consecutive non-replicate clinical isolates of carbapenem non-susceptible (resistant or intermediate) Enterobacteriaceae (n=191) were collected from 21 Italian hospital laboratories between November 2013 and April 2014. Most isolates 178 (93%) were KPC-KP, with 76 (43%) respectively resistant to colistin. This report details the findings and discusses potential implications for infection control.
Predictive Models for Identifying Patients Infected with KPC-producing *K. pneumoniae*

- Retrospective, 1:2 matched case control study in 5 Italian centers
- 657 patients with clinical samples of KPC-Kp
  - 426 patients with KPC-Kp infections

Independent Predictors

KPC-Kp Isolation

- Recent admission to the ICU
- Indwell. urinary catheter
- CVC and/or surgical drain
- >2 recent hospitalization
- Hematological cancer
- Recent FQ and/or carbapenem tx

Infection with KPC-Kp

- Charlson index ≥3
- CVC
- Recent surgery
- Neutropenia
- >2 recent hospitalization
- Recent FQ and/or carbapenem tx

## KPC-Kp in Hematological Malignancies

<table>
<thead>
<tr>
<th>Year</th>
<th>Any Gram (-)</th>
<th>Non-KPC-Kp</th>
<th>KPC-Kp</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BSI, n</td>
<td>Deaths, n (%)</td>
<td>BSI, n</td>
</tr>
<tr>
<td>2009</td>
<td>30</td>
<td>5 (16.6)</td>
<td>1</td>
</tr>
<tr>
<td>2010</td>
<td>39</td>
<td>7 (17.9)</td>
<td>2</td>
</tr>
<tr>
<td>2011</td>
<td>41</td>
<td>9 (24.3)</td>
<td>5</td>
</tr>
<tr>
<td>2012</td>
<td>47</td>
<td>11 (29.7)</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>147</td>
<td>32 (21.7)</td>
<td>12</td>
</tr>
</tbody>
</table>

Infections by CRKp in SCT Recipients
Italy 2010-2013

- Retrospective survey in 52 Italian Centers
  - 53.4% centers reported CRKp infections
    - 25 auto-SCT (0.4%) (0.1% in 2010 to 0.7% in 2013)
    - 87 allo-SCT (2%) (0.4% in 2010 to 2.9 in 2013)

- Infection followed colonization in
  - 25.8% in auto
  - 39.2% in allo

Infections by CRKp in SCT Recipients
Italy 2010-2013

- Infection-related mortality
  - 16% in auto
  - 64.4% in allo

- Independent risk factors for mortality in allo patients
  - Pre-transplant CRKp infection
  - A non-CRKp-targeted 1st line treatment

## Alternatives to Carbapenemams for Infections Caused by ESBL-producers

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin</td>
<td>Neprotoxicity, poor outcomes in pneumonia, no activity for <em>Proteus</em> and <em>Serratia</em>, R in <em>K. pneumoniae</em> reported</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>No activity for <em>P. aeruginosa</em>, <em>Proteus</em>, <em>Morganella</em>. Not effective in VAP</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>Risk of mutational resistance. Few data for iv form.</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Only for lower UTI</td>
</tr>
<tr>
<td>Beta-lactamase inhibitors</td>
<td>Many ESBL producers and all carbapenemase producers are resistant</td>
</tr>
<tr>
<td>Aminoglycosides, quinolones,</td>
<td>Many ESBL producers and all carbapenemase producers are resistant</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td></td>
</tr>
</tbody>
</table>

Hawkey & Livermore BMJ 2012;344:e3236
Bacterial Resistance in Haematology-ECIL 4
Study Groups & Participants

• Epidemiology & resistance
  – M Mikulśka*, M Akova, D Averbuch, G Klyasova, Livermore, C Orasch, M Tumbarello
  – DM

• Empirical & targeted antibacterial therapy
  – D Averbuch*, C Cordonnier, WV Kern, C Viscoli

• Duration of antibacterial therapy
  – C Orasch*, G Klyasova, P Munoz

• Antibiotic stewardship
  – IC Gyssens*, WV Kern, DM Livermore

Group leader: Murat AKOVA
Meeting: September 8-10th, 2011
Final version: Feb 14th, 2012

* Presenting authors

4th European Conference on Infections in Leukemia
European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia

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ABSTRACT

Owing to increasing resistance and the limited arsenal of new antibiotics, especially against Gram-negative pathogens, carefully designed antibiotic regimens are obligatory for febrile neutropenic patients, along with effective infection control. The Expert Group of the 4th European Conference on Infections in Leukemia has developed guidelines for initial empirical therapy in febrile neutropenic patients, based on: i) the local resistance epidemiology; and ii) the patient's risk factors for resistant bacteria and for a complicated clinical course. An ‘escalation’ approach, avoiding empirical carbapenem and combinations, should be employed in patients without particular risk factors. A ‘de-escalation’ approach, with initial broad-spectrum antibiotics or combinations, should be used only in those patients with: i) known prior colonization or infection with resistant pathogens; or ii) complicated presentation; or iii) in centers where resistant pathogens are prevalent at the onset of febrile neutropenia. In the latter case, infection control and antibiotic stewardship also need urgent review. Modification of the initial regimen at 72-96 h should be based on the patient's clinical course and the microbiological results. Discontinuation of antibiotics after 72 h or later should be considered in neutropenic patients with fever of unknown origin who are hemodynamically stable since presentation and afebrile for at least 48 h, irrespective of neutrophil count and expected duration of neutropenia. This strategy aims to minimize the collateral damage associated with antibiotic overuse, and the further selection of resistance.
Escalation Approach for Empirical Therapy in High Risk Patients-

• Indications (BII)
  – Uncomplicated presentation
  – No colonization or previous infection with R bacteria
  – In centers where R bacteria are rare

• Options for initial therapy
  – Anti-pseudomonal cephalosporin (AI)
  – Piperacillin-tazobactam (AI)
  – Ticarcillin-clavulanate, sulbactam-cefoperazon, piperacillin + gentamicin

De-escalation Approach

• **Indications (BII)**
  - Complicated presentation
  - Known colonization or previous infection with R bacteria
  - In centers where R bacteria are prevalent

• **Options for initial therapy**
  - Carbapenem monotherapy (BII)
  - Combination therapy including early coverage for R Gram (+)ves

When Carbapenems Should be the 1st Choice?

• Patients with septic shock (BII)
• Know colonization or previous infection with (BII)
  – ESBL (+) enterics
  – Gram (-)ves R to narrow spectrum B-lactams
  – Centers with high prevalence of infections with ESBL (+)ves

When Aminoglycoside Combinations are Indicated? BII

- Seriously ill patients
- If R non-fermenters are likely
  - Local epidemiology
  - Previous colonization or infection
  - Use of carbapenems during the last month

A Zen Garden in Kyoto
15 Rocks Surrounded by Gravel

- One cannot see all 15 rocks from any point
- There always will be in need of another perspective
"Zen" Approach to Empirical Therapy in Febrile Neutropenia in an MDR Setting

• Data on local resistance prevalence
• Consider PK/PK parameters
• Consider combination antibiotics where MDR is prevalent
• De-escalate when susceptibility is known
• Do not over treat
Thank you...