Emerging bacterial resistance and impact on empirical therapy in cancer

Claudio Viscoli, MD
Professor of Infectious Disease
University of Genova, Italy
Potential conflicts of interest

• Received grants as speaker/moderator in national or international meetings sponsored by Pfizer, Gilead, MSD, Astellas, Abbott, BMS, Novartis

• Received grants for participation in national or international advisory boards by Gilead, Astellas, MSD, Pfizer, Novartis

• Obtained research grants for my institution from Pfizer, MSD, Gilead, Abbott, Jansen, BMS, Novartis

• Expert for the SAG (Scientific Advisory Group) for antibacterials and antifungals of CHMP-EMA and consultant for Italian Medical Drug Agency

• Member of several local boards (Genoa, Liguria, Italy and my hospital) (Hospital Infection Control and Antibiotic Stewardship, HIV, vaccination, Hospital Formulary)
Topics for discussion

- Classic empirical therapy
- Present general and specific (for hematology) epidemiological situation
- Impact on survival
- Empirical therapy in 2014
Traditional antibacterial approach to the high risk neutropenic patient

- Universal FQ prophylaxis
- If fever, start with a III gen cephalosporin or piperacillin-tazobactam
- Combining an aminoglycoside not recommended
- Add a glycopeptide on day 3 if persistent fever (an approach not validated by RCT)
- Keep carbapenems as second-line therapy
- Adjust therapy based on cultural results
Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,1 Eric J. Bow,9 Kent A. Sepkowitz,2 Michael J. Bodeck,4 James I. Ito,5 Craig A. Mullen,3 Issam I. Raad,6 Kenneth V. Rolston,6 Jo-Anne H. Young,7 and John R. Wingard8

2011
Fever ($\geq 38.3^\circ C$) and Neutropenia ($\leq 0.5 \times 10^9$ cells/L)

**LOW RISK**
- Anticipated neutropenia ≤ 7 days and clinically stable and no medical comorbidities

**OUTPATIENT ANTIBIOTICS**
- Oral regimen if able to tolerate and absorb
- Availability of caregiver, telephone, transportation
- Patient & physician decision

- Oral ciprofloxacin + amoxicillin/clavulanate

- Observe 4-24 hours in clinic to ensure that empiric antibiotics are tolerated and patient remains stable prior to discharge for outpatient therapy.

**INPATIENT IV ANTIBIOTICS**
- Documented infection requiring IV antibiotics
- Gastrointestinal intolerance
- Patient & physician decision

If responding and criteria met for outpatient management (see text)

Adjust antimicrobials based on specific clinical, radiograph and/or culture data, for example:
- Vancomycin or linezolid for cellulitis or pneumonia
- Add aminoglycoside and switch to carbapenem for pneumonia or gram negative bacteremia
- Metronidazole for abdominal symptoms or suspected C. difficile infection

**HIGH RISK**
- Anticipated neutropenia > 7 days or
- Clinically unstable or
- Any medical comorbidities

**INPATIENT IV ANTIBIOTICS**
- Empiric antibiotic monotherapy (any of the following):
  - Piperacillin/tazobactam or
  - Carbapenem or
  - Ceftazidime or
  - Cefepime
Single-Organisms Bacteremias
EORTC-IATG Trials

Percent of Febrile Episodes

Gram-negative
Gram-positive

1973-76
'77-’80
'80-’83
'83-’85
'86-’88
'88-’91
'91-’92
'93-’94
'97-’00
Mortality rate in pts. with SGP bacteremias randomised in IATG-EORTC trials (1985-2000)

P = 0.009 (for trend)

Overall mortality
Mortality from infection

P = 0.58
Topics for discussion

• Classic empirical therapy
• Present general and specific (for hematology) epidemiological situation
• Impact on survival
• Empirical therapy in 2014 between ESBL, carbapenemase, etc
EARSS-NET

European Centre for Disease Prevention and Control
Proportion of 3rd gen. cephalosporin-resistant ESBL-producer *Escherichia coli*
Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases

L. Silvia Munoz-Price, Laurent Poirel, Robert A Bonomo, Mitchell J Schwaber, George L Daikos, Martin Cormican, Giuseppe Cornaglia, Javier Garau, Marek Gniadkowski, Mary K Hayden, Karthikeyan Kumarasamy, David M Livermore, Juan J Mayo, Patrice Nordmann, Jean B Patel, David L Paterson, Johann Pitout, Maria Virginia Villegas, Hui Wang, Neil Woodford, John P Quinn

*Lancet Inf Dis* 2013

**Figure:** Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin. Other carbapenemase types include VIM, OXA-48, or NDM. KPC = *Klebsiella pneumoniae* carbapenemase.
Proportion of CRKP in Europe

- 2006
- 2008
- 2010
- 2012

ESCMID Online Lecture Library
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Proportion of carbapenem-resistant *Pseudomonas aeruginosa*
Enterococchi R against vancomicina, 2011

Malgorzata Mikulska, Valerio Del Bono, Anna Maria Raiola, Barbara Bruno, Francesca Gualandi, Domenico Occhini, Carmen di Grazia, Francesco Frassoni, Andrea Bacigalupo, Claudio Viscoli

168 episodes of BSI
HSCT – Genova Italy
Pre-engraftment BSI 2008-2013

159 episodes of pre-engraftment BSI diagnosed in 129/489 patients (26.4%), with 23 patients experiencing more than 1 BSI (4.7%)

171 pathogens isolated (more than one isolated pathogen in 12 episodes)
163/171 bacterial (95%)
8/171 fungal (5%)
• 55% Gram positive vs 40% Gram negative
• Gram+/Gram- ratio did not differ in primary and secondary episodes of BSI
Decrease in the resistance of staphylococci to methicillin was the only significant susceptibility change compared to the previous observation period and during the study years 2008-2013.
Aetiology and resistance in bacteraemias among adult and paediatric haematology and cancer patients

Małgorzata Mikulska, Claudio Viscoli, Christina Orasch, David M. Livermore, Diana Averbuch, Catherine Cordinnier, Murat Akova, on behalf of the Fourth European Conference on Infections in Leukemia Group (ECIL-4), a joint venture of EBMT, EORTC, ICHS, ELN and ESGICH/ESCMID
Figure 1. Aetiology of bacteraemias (median prevalence with range) reported in the ECIL-4 questionnaire survey. Notes: CNS, coagulase negative staphylococci.
<table>
<thead>
<tr>
<th>Causative organisms</th>
<th>First period n = 272 (%)</th>
<th>Second period n = 283 (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive bacteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>10 (6)</td>
<td>14 (12)</td>
<td></td>
</tr>
<tr>
<td>Methicillin-resistant <em>S. aureus</em></td>
<td>1 (17)(^a)</td>
<td>4 (28.6)(^a)</td>
<td></td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>81 (46.5)</td>
<td>50 (43)</td>
<td></td>
</tr>
<tr>
<td>Corynebacterium spp.</td>
<td>8 (5)</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>Viridans group streptococci</td>
<td>71 (42)</td>
<td>22 (23)</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>6 (3)</td>
<td>7 (6)</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
<td>10 (6)</td>
<td>26 (23)</td>
<td></td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td>3 (30)(^b)</td>
<td>10 (38.5)(^b)</td>
<td></td>
</tr>
<tr>
<td><em>E. faecium</em></td>
<td>6 (60)(^b)</td>
<td>13 (50)(^b)</td>
<td></td>
</tr>
<tr>
<td><em>E. gallinarum</em></td>
<td>1 (10)(^b)</td>
<td>3 (11.5)(^b)</td>
<td></td>
</tr>
<tr>
<td>Gram-negative bacteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>75 (28)</td>
<td>138 (49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>20 (27)</td>
<td>32 (23)</td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>5 (7)</td>
<td>31 (22)</td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella oxytoca</em></td>
<td>0</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>0</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td>6 (7)</td>
<td>12 (9)</td>
<td></td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>1 (1)</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
<td>0</td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td>Multi-drug-resistant</td>
<td>2 (3)</td>
<td>16 (11)</td>
<td>0.04</td>
</tr>
<tr>
<td>gram-negative bacilli</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
<td>5 (2)</td>
<td>8 (3)</td>
<td>0.57</td>
</tr>
<tr>
<td>Prevotella spp.</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><em>Fusobacterium</em> spp.</td>
<td>2 (40)</td>
<td>4 (50)</td>
<td></td>
</tr>
<tr>
<td><em>Bacteroides</em> spp.</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><em>Clostridium</em> spp.</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Fungi</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida tropicalis</em></td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><em>Candida glabrata</em></td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><em>Candida krusei</em></td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><em>Candida parapsilosis</em></td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><em>Fusarium solani</em></td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Polymicrobial bacteraeimia(^d)</td>
<td>35 (13)</td>
<td>26 (9)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

\(^a\) With no significant differences between both periods.

\(^b\) With significant differences between both periods.
Topics for discussion

• Classic empirical therapy
• Present general and specific (for hematology) epidemiological situation
• Impact on survival
• Empirical therapy in 2014 between ESBL, carbapenemase, etc
2008-2010 vs. 2011-2013

G+/G- ratio

2008-2010 (n=229) vs 2011-2013 (n=260)

<table>
<thead>
<tr>
<th>G+/G- ratio</th>
<th>2008-2010 (%)</th>
<th>2011-2013 (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>G+</td>
<td>65%</td>
<td>51%</td>
<td>0.15</td>
</tr>
<tr>
<td>G-</td>
<td>35%</td>
<td>49%</td>
<td></td>
</tr>
</tbody>
</table>

Incidence of BSI

<table>
<thead>
<tr>
<th>Incidence</th>
<th>2008-2010 (%)</th>
<th>2011-2013 (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSI</td>
<td>22%</td>
<td>30%</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Post-BSI 7d mortality

<table>
<thead>
<tr>
<th>Mortality</th>
<th>2008-2010 (%)</th>
<th>2011-2013 (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-BSI</td>
<td>12%</td>
<td>3%</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Post-BSI 30d mortality

<table>
<thead>
<tr>
<th>Mortality</th>
<th>2008-2010 (%)</th>
<th>2011-2013 (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-BSI</td>
<td>28%</td>
<td>9%</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Aim: identify risk factors for mortality in patients with haematological malignancies with E. coli bacteremia

Retrospective, 8-year study

- 62 E. coli BSI
- ESBL production - 41.9%, fluoroquinolone resistance 62.9%
- 36 different ESBL genes were identified in 26 ESBL+ isolates
- 9 strains carried multiple ESBLs
- 30-day mortality rate was 20.9% (13/62)
- Predictors of mortality were: inadequate initial antimicrobial therapy, ESBL+ and prolonged neutropenia
Factors associated with mortality in bacteremic patients with hematologic malignancies

Mario Tumbarello\textsuperscript{a, *}, Teresa Spanu\textsuperscript{b}, Morena Caira\textsuperscript{c}, Enrico M. Trecarichi\textsuperscript{a}
Luca Laurenti\textsuperscript{c}, Eva Montuori\textsuperscript{a}, Luana Fianchi\textsuperscript{c}, Fiammetta Leone\textsuperscript{b},
Giovanni Fadda\textsuperscript{b}, Roberto Cauda\textsuperscript{a}, Livio Pagano\textsuperscript{c}

\textsuperscript{a}Institute of Infectious Diseases, Catholic University of the Sacred Heart, Largo A. Gemelli 8, 00168 Rome, Italy
\textsuperscript{b}Institute of Microbiology, Catholic University of the Sacred Heart, Largo A. Gemelli 8, 00168 Rome, Italy
\textsuperscript{c}Institute of Hematology, Catholic University of the Sacred Heart, Largo A. Gemelli 8, 00168 Rome, Italy

Received 9 June 2008; accepted 17 February 2009

Table 3
Multivariate analysis of factors associated with death at 30 days among patients with hematologic malignancies and bacteremia

<table>
<thead>
<tr>
<th>Variable</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia ≥10 days at bacteremia onset</td>
<td>&lt;0.001</td>
<td>6.07 (2.66–13.82)</td>
</tr>
<tr>
<td>Presentation with acute renal failure</td>
<td>0.002</td>
<td>5.62 (1.88–16.77)</td>
</tr>
<tr>
<td>Nosocomial bacteremia</td>
<td>0.009</td>
<td>4.22 (1.43–12.41)</td>
</tr>
<tr>
<td>Age &gt;55 years</td>
<td>0.007</td>
<td>3.40 (1.40–8.24)</td>
</tr>
<tr>
<td>Monomicrobial bacteremia due to AR</td>
<td>0.009</td>
<td>3.15 (1.32–7.50)</td>
</tr>
<tr>
<td>Gram negative organisms</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Slide withheld at request of author
Slide withheld at request of author
Slide withheld at request of author
Topics for discussion

- Classic empirical therapy
- Present general and specific (for hematology) epidemiological situation
- Impact on survival
- Empirical therapy in 2014 between ESBL, carbapenemase, etc
The big dilemma

• III gen cephalosporins and pip-tazo do not work any more in many centers because of the ESBL production by many Gram neg rods; mortality is increasing, especially if inadequate initial therapy

• Carbapenem-based empirical therapy would the logical consequence, but a large use of carbapenems induce carbapenemase production

• Carbapenemase-producing Enterobacteriaceae infections associated with high mortality, again especially if inadequate initial therapy
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

Diana Averbuch,1 Christina Orasch,2 Catherine Cordonnier,3 David M. Livermore,4 Małgorzata Mikulska,5 Claudio Viscoli,5 Inge C. Gyssens,6,7,8 Winfried V. Kern,9 Galina Klyasova,10 Oscar Marchetti,2 Dan Engelhard,1 and Murat Akova;11 on behalf of ECIL4, a joint venture of EBMT, EORTC, ICHS, ESGICH/ESCMID and ELN
Factors in choosing a regimen

• Local bacterial epidemiology and resistance patterns

• Patient’s prior colonization or infection by resistant pathogens, particularly:
  – MRSA, with vancomycin MICs >2 mg/L
  – Vancomycin-resistant enterococci
  – ESBL- or carbapenemase-producing Enterobacteriaceae
  – A. baumannii, P. aeruginosa & S. maltophilia
  – KPC

• Other patient-related factors
  – Other risk factors for infection due to resistant pathogens
  – Clinical presentation
Introducing de-escalation therapy in the management of febrile neutropenia?

**Defining de-escalation**

Initial empirical regimen is very broad, with coverage of multi-resistant Gram +ve and –ve pathogens (e.g. ESBL-producers) e.g. carbapenem + anti-MRSA agent

Therapy is de-escalated to a simpler or narrower spectrum (‘targeted’) therapy if no pathogen or no resistant pathogen is isolated.
### Table 3. ECIL-4 recommendation for initial empirical treatment in high-risk patients (anticipated to have neutropenia for more than 7 days), by indication and escalation or de-escalation approach.

<table>
<thead>
<tr>
<th>Escalation approach</th>
<th>De-escalation approach</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication B-II for all</strong></td>
<td><strong>Indication B-II for all</strong></td>
</tr>
<tr>
<td>1) Uncomplicated presentation;</td>
<td>1) Complicated presentations;</td>
</tr>
<tr>
<td>2) No known colonization with resistant bacteria;</td>
<td>2) Known colonization with resistant bacteria;</td>
</tr>
<tr>
<td>3) No previous infection with resistant bacteria;</td>
<td>3) Previous infection with resistant bacteria;</td>
</tr>
<tr>
<td>4) In centers where infections due to resistant pathogens are rarely seen at the onset of febrile neutropenia;</td>
<td>4) In centers where resistant pathogens are regularly seen at the onset of febrile neutropenia;</td>
</tr>
</tbody>
</table>

**Options for initial antibiotic therapy**

1) Anti-pseudomonal cephalosporin (cefepime*, ceftazidime*) AI
2) Piperacillin-tazobactam AI
3) Other possible options include*:
   - Ticarcillin-clavulanate*
   - Ceftoperazone-suubactam*
   - Piperacillin + gentamicin*

1) Carbapenem monotherapy BII
2) Combination of anti-pseudomonal β–lactam + aminoglycoside or quinolone* (with carbapenem as the β–lactam in seriously ill patients) BIII
3) Colistin + β–lactam + rifampicin BIII*
4) Early coverage of resistant-Gram-positives with a glycopeptide or newer agent (If risk factors for Gram-positives present) CIII
In patients with **unexplained fever** it is recommended that the initial regimen be continued until there are clear signs of marrow recovery; the traditional endpoint is an **increasing ANC that exceeds 500 cells/mm³** B-II

In clinically documented infection (CDI) or microbiologically documented infection (MDI): duration dictated by particular organism or site; appropriate antibiotics should continue for **at least the duration of neutropenia** (until ANC ≥ 500 cells/mm³) or longer if necessary B-III

**Alternatively**, if an appropriate treatment course has been completed and **all signs and symptoms of a CDI or MDI have resolved**, patients who remain neutropenic may **resume oral fluoroquinolone prophylaxis** until marrow recovery C-III
Duration of antibacterial treatment

Empirical antibiotics can be discontinued after 72 h or more of intravenous administration in patients who have been hemodynamically stable since presentation and have been afebrile for 48 h or more, irrespective of their neutrophil count or expected duration of neutropenia BII. The patient should be kept hospitalized under close observation for at least a further 24-48 h if the patient is still neutropenic when antibiotic therapy is stopped. If fever recurs, antibiotics should be re-started urgently, after obtaining blood cultures and clinical evaluation. Centers that give prophylactic antibacterial agents should consider renewing this regimen upon discontinuation of the empirical therapy if the patient is still neutropenic CIII.

Duration of antibacterial-targeted treatment in MDI with or without bacteremia is described in the companion manuscript in this issue of the Journal.
Conclusion

- The phenomenon of antibiotic resistance is posing new and dramatic problems in every field of medicine and surgery, incl. Hematology
- Decreasing the use of antibiotics is mandatory
- New approaches are necessary, since we cannot rely anymore on a «one size fits all» criterion
- Classical escalation therapy with III gen cephalosporins or pip-tazo still best choice in many hospitals, but strict surveillance indispensable
- De-escalation therapy, starting with a carbapenem or even with aggressive anti-KPC combinations might be recommendable, depending on local epidemiology and patient-related factors
- Most of the indications given in guidelines have poor grading of scientific evidence: urgent need of new studies
Thank you for your attention