Incidence of infections in acute non-lymphocytic leukemia during induction therapy

Granulocyte count (cells/μl)
Febrile neutropenia
some figures

 Incidence :
  - Leukemia and HSCT : 80% - 90 
  - Solid tumor or lymphoma : 5 – 8 

 Mortality :
  - Overall :
    - Solid tumors : 9.5 
    - Lymphoma and leukemia : 14 
  - Infection-related :
    - Solid tumors : 2.3 
    - Lymphoma and leukemia : 5 

Bucaneve et al, NEJM 2005;353:977-987
Cullen et al, NEJM 2005;353:988-998
Risk model for mortality in hospitalized cancer patients with FN

- A multivariate model with risk factors for mortality including:
  - Age $\geq$ 65
  - Cancer type (leukemia, lung cancer)
  - Comorbidities (CHF, PE, lung, renal, liver, and cerebrovascular disease)
  - Infectious complications (hypotension, pneumonia, bacteremia and fungal infection)

Kuderer NM et al, J Clin Oncol 2004
Prediction of mortality

- Two recent studies have reported hypotension and bacteremia as significant risk factors for prolonged hospitalization and high mortality.
- Malik et al reported a mortality rate associated with FN in patients presenting with shock of 82%.
- Darmon et al reported that patients admitted to an ICU with FN experienced a 54% 30-day mortality.

Malik I et al; J Infect 2001
Darmon M et al; Intensive Care Med 2002
Causes of fever during neutropenia

CDI: clinically documented infections
MDI: microbiologically documented infections
FUO: fever of unknown origin
FNIO: fever of non-infectious origin

From Toussaint et al, Supp Care in Cancer 2006
Sites of involvement and microbial pathogens

**Oral mucositis**

- Oral flora: v. Streptococci,
  Fusobacterium,
  Stomatococcus,
  Rothia dentocariosa,
  Capnocytophaga,
  Eikenella corrodens
  Bacteroides oralis (necrotizing gingivitis)
- HSV, Candida sp (concomitant esophagitis)
Sites of involvement and microbial pathogens

**Typhlitis**

- Clostridium septicum
  - Other clostridia
  - Enterobacteriaceae
  - Bacteroides fragilis
  - Candida spp.
Sites of involvement and microbial pathogens

**Perianal abscess**

Polymicrobial:
- GNB (E.coli),
- Anaerobes (B. fragilis)
- Enterococci
Sites of involvement and microbial pathogens

**Short duration of neutropenia (N<7 days)**
- Conventional bacteria (70% associated bacteremia)
  - S. pneumoniae
  - H. influenzae
  - Enterobacteriaceae
  - P. aeruginosa

**Long duration of neutropenia (N>7 days)**
- Multiresistant organisms
  - ESBL or AmpC GNB
  - Multiresistant P. aeruginosa
- Fungi
  - Aspergillus, Mucor, Fusarium

Aoun M. Médisphère 1999
Percentage of all granulocytopenic patients who developed invasive pulmonary aspergillosis (IPA) as a function of duration of granulocytopenia. Two linear regression lines were calculated: one between the 1st and 22nd days, $y = 1.0X - 4.0$; the other between the 22nd and 36th days, $y = 4.3X + 73$.

Gerson et al., 1984
Proven or probable aspergillosis
Institut J. Bordet

April 2002 – December 2005

NF : 2/17 (11,7%)
F : 5/47 (10,6%)
Haplo : 5/23 (21,7%)
Invasive aspergillosis: clinical manifestations

Persistent fever

- Pneumonia: - Pleuritic chest pain
  - Cough
  - Dyspnea and hypoxia

- Sinusitis: - Nasal discharge
  - Epistaxis
  - Facial swelling and tenderness
Bloodstream infections in FN patients

- Incidence ~ 25 – 30%
- Increased mortality:
  - Bacteremic vs non-bacteremic (10 vs 3%)
  - GNB vs GPB (18 vs 5%)
  - Polymicrobial (13%)
  - Complex vs primary (12 vs 8%)
- Common pathogens:
  - Common Gram-positive pathogens
    - CNS, MSSA or MRSA, Enterococcus spp., S. viridans group, S. pneumoniae, S. pyogenes
  - Common Gram-negative pathogens:
    - E. coli, Klebsiella spp, Enterobacter spp, P. aeruginosa, Citrobacter spp., Acinetobacter spp., S. maltophilia

Frere et al, Bone Marrow Transplant 2006; 37:411-418
Single-Organisms Bacteremias in EORTC-IATG Trials of empirical therapy of febrile neutropenia

% of febrile episodes

- Gram negative
- Gram positive

Non resorbable ABs
- TMP-SMZ
- Nalidixic acid
- fluoroquinolones

Indwelling catheters

Years:
- 1973-76
- ‘77-’80
- ‘80-’83
- ‘83-’85
- ‘86-’88
- ‘88-’91
- ‘91-’92
- ‘93-’94
- ‘97-’00

EORTC IATG
Major elements of standard care

- Empiric therapy
- Double coverage with β-lactam and an aminoglycoside
- β-lactam monotherapy
- Risk-adapted therapy
Single-drug therapy

First line
- Ceftazidime
- Cefepime
- Piperacillin/tazobactam

Second line
Carbapenems:
- Imipenem
- Meropenem
## Distribution of etiologic agent isolated from bacteremia in patients with cancer in published studies since 2008

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Country</strong></td>
<td>Pakistan</td>
<td>Italy</td>
<td>Sweden</td>
<td>Japan</td>
<td>South Korea</td>
<td>Spain</td>
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<tr>
<td><strong>Prophylaxis</strong></td>
<td>Not reported</td>
<td>Not reported</td>
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<td>No prophylaxis</td>
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<td>No prophylaxis</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>P. aeruginosa</td>
<td>9.7 %</td>
<td>15 %</td>
<td>5.3 %</td>
<td>14.7 %</td>
<td>7.1 %</td>
<td>23 %</td>
</tr>
<tr>
<td>E. coli</td>
<td>36.6 %</td>
<td>NS</td>
<td>17.8 %</td>
<td>18.6 %</td>
<td>25 %</td>
<td>51 %</td>
</tr>
<tr>
<td>S. maltophilia</td>
<td>2 %</td>
<td>NS</td>
<td>0.8 %</td>
<td>NS</td>
<td>NS</td>
<td>1%</td>
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<td>Acinetobacter spp.</td>
<td>14.8 %</td>
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<td>1 %</td>
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<td>Klebsiella spp.</td>
<td>11.6 %</td>
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<td>9 %</td>
<td>16.2 %</td>
<td>22 %</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>8.5 %</td>
<td>NS</td>
<td>5.4 %</td>
<td>3.5 %</td>
<td>4.7 %</td>
<td>9 %</td>
</tr>
<tr>
<td>Citrobacter spp.</td>
<td>1.7 %</td>
<td>NS</td>
<td>1.3 %</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td><strong>Gram positive</strong></td>
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</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>55.2 %</td>
<td>NS</td>
<td>NS</td>
<td>33 %</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Staphylococcus aureus</td>
<td>9.5 %</td>
<td>NS</td>
<td>6.9 %</td>
<td>1.3 %</td>
<td>NS</td>
<td>9.8 %</td>
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<tr>
<td>Coagulase-negative staph.</td>
<td>5.1 %</td>
<td>NS</td>
<td>14.7 %</td>
<td>23.1 %</td>
<td>NS</td>
<td>8.3 %</td>
</tr>
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<td>5.8 %</td>
<td>9.2 %</td>
<td>23 %</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>3.5 %</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>3.4 %</td>
<td>NS</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>3.5 %</td>
<td>NS</td>
<td>2.3 %</td>
<td>NS</td>
<td>2 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Streptococcus viridans</td>
<td>3.5 %</td>
<td>NS</td>
<td>14 %</td>
<td>5.8 %</td>
<td>NS</td>
<td>23 %</td>
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</table>
Neutropenic adult patient with hematological malignancies or HSCT

<table>
<thead>
<tr>
<th>Organism</th>
<th>Total</th>
<th>%</th>
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<tr>
<td><strong>Single Gram-negative</strong></td>
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<tr>
<td>Single Gram-negative</td>
<td>83</td>
<td>40</td>
</tr>
<tr>
<td>E. coli</td>
<td>47</td>
<td>22.7</td>
</tr>
<tr>
<td>P. Aeruginosa</td>
<td>17</td>
<td>8.2</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>17</td>
<td>8.2</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>S. maltophilia</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Single Gram-positive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>40</td>
</tr>
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<td>Streptococcus viridans</td>
<td>34</td>
<td>16.4</td>
</tr>
<tr>
<td>Enterococcus sp.</td>
<td>17</td>
<td>8.2</td>
</tr>
<tr>
<td>Staphylococcus coagulase negative</td>
<td>20</td>
<td>9.6</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>4</td>
<td>1.9</td>
</tr>
<tr>
<td>others</td>
<td>8</td>
<td>3.8</td>
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<tr>
<td>**Polymicrobial **</td>
<td></td>
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<tr>
<td>Polymicrobial *</td>
<td>32</td>
<td>15.5</td>
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<tr>
<td><strong>anaerobes</strong></td>
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<tr>
<td>anaerobes</td>
<td>7</td>
<td>3.4</td>
</tr>
<tr>
<td><strong>yeasts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yeasts</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

* Mixed GNB : 9; mixed GPB : 12; mixed GNB+GPB : 11
Neutropenic adult patient with hematological malignancies or HSCT

- 110 (47.8%)
- 111 (48.2%)
- 7
- 2

BGN
BGP
Anaerobes
Yeasts
Enterococcus faecium
S. aureus
Klebsiella pneumoniae
Acinetobacter baumanii
P. aeruginosa
Enterobacter sp.

Enterococcus faecium
S. aureus (S. viridans)
Clostridium difficile
Acinetobacter sp.
P. aeruginosa
Enterobacteriaceae
S. maltophilia

Rice LB, JID 2008;197-1079
Bacteremia due to multidrug-resistant gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes

- of 747 bacteremias (2006-2009), 372 were due to GNB
- 51 of 372 (13.7%) were caused by MDRGNB

MDRGNB risk factor for 30-day mortality (OR 3.5, 95% CI 1.4-9.1)
- ESBL-Enterobacteriaceae
- Amp-C-Enterobacteriaceae
- S. maltophilia
- A. baumannii
- P. aeruginosa
- other

Gudiol C, J Antimicrob Chemother 2011
### Institut Jules Bordet
Bacteremias 2008-2012
N=230 pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>ESCAPES</th>
<th>rESCAPES</th>
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<tbody>
<tr>
<td>E.coli</td>
<td>60</td>
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<td>6</td>
</tr>
<tr>
<td>Acinetobacter sp</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S. maltophilia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>S. viridans</td>
<td>42</td>
<td>1 (pen R) 5 (pen I)</td>
</tr>
<tr>
<td>Enterococcus sp</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>S. aureus</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Risk of resistant pathogen : 15.46%
Global distribution of CTX-M genotypes.11,13,15,62–84.

Faecal isolates
a Lebanon, b Israel, c Kuwait

Hawkey PM; JAC 2009;64 suppl 1:i3-i10
### CTX-M ESBL

<table>
<thead>
<tr>
<th>Classes</th>
<th>Genes</th>
</tr>
</thead>
</table>
| Aminoglycosides | *aac6' –lb-cr*  
*aadA5*            |
| ß-lactams      | *bla*<sub>CTX-M-15</sub>, *bla*<sub>OXA-1</sub>  
*bla*<sub>TEM-1</sub> |
| Chloramphenicol| *catB4*                            |
| Macrolides     | *mph(A)*                           |
| Fluoroquinolones | *aac6' –lb-cr*                      |
| Sulphonamides  | *sull*                             |
| Trimethoprim   | *dhfr<sub>XVII</sub>*              |
| Tetracycline   | *tet(A)*                           |

ESBL(s)  
Klebsiella spp. and E. coli

- Prevalence varies with
  - Geographical area, institution, unit

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication Year</th>
<th>Country</th>
<th>Organisms</th>
<th>Prevalence</th>
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</thead>
<tbody>
<tr>
<td>Ortega</td>
<td>JAC 2009</td>
<td>Spain</td>
<td>E. coli</td>
<td>4 %</td>
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<tr>
<td>Gudiol</td>
<td>JAC 2010</td>
<td>Spain</td>
<td>E. coli</td>
<td>12.6%</td>
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<tr>
<td>Si-Hoyn Kim</td>
<td>Ann Hematol 2013</td>
<td>Korea</td>
<td>E. coli+K. pneumoniae</td>
<td>26 %</td>
</tr>
<tr>
<td>Chiol-In Kang</td>
<td>Ann Hematol 2012</td>
<td>Korea</td>
<td>E.coli+K. pneumoniae</td>
<td>23 %</td>
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<td>Tumbarello</td>
<td>AAC 2006</td>
<td>Italy</td>
<td>K. pneumoniae</td>
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<td>Trecarichi</td>
<td>J Infection 2009</td>
<td>Italy</td>
<td>E.coli</td>
<td>41%</td>
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<tr>
<td>Kara Ö</td>
<td>ICAAC 2010</td>
<td>Turkey</td>
<td>E.Coli+K. pneumoniae</td>
<td>40%-25%</td>
</tr>
</tbody>
</table>
Institut Jules Bordet
Bacteremias 2008-2012
N=230 pathogens

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<td>3</td>
<td>2</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Acinetobacter sp</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S. maltophilia</td>
<td>1</td>
<td>0</td>
</tr>
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</table>

Risk of resistant pathogen : 15.46%
Worldwide and European geographic distribution of Verona integron-encoded metallo-β-lactamase (VIM) and IMP enterobact

Nordmann P et al, Emerging Infectious Diseases 2011;17
Worldwide geographic distribution of *Klebsiella pneumoniae* carbapenemase (KPC)

Nordmann P et al, Emerging Infectious Diseases 2011;17
Geographic distribution of oxacillinase-48 (OXA-48)
Geographic distribution of New Delhi metallo-β-lactamase-1 (NDM-1)

Nordmann P et al, Emerging Infectious Diseases 2011;17
Fecal carriage of NDM-1 in hospitalized and non hospitalized patient

- 122 healthy controls and 95 ICU patients
- Fecal carriage was seen
  - 9/122 (7.4%) of controls
  - 25/95 (27.4%) of ICU patients carbapenem resistance
  - Day 1- 3/95 (3.2%)
  - Day 4- 13/97 (13.7%)
  - 8/95 (8.4%) showed colonisation on both days
  - Mainly E. coli, Mainly NDM-1

- 7.4 % controls
- ICU
  - Day 1-3.2%
  - Day 4-13.7%

HISICON 2013 abstract OC 17
G. Mittal et al, Vardhaman Mahavir Medical College & Safdarjung Hospital, Delhi
Depuis le début de la surveillance, le nombre absolu de patients CPE-positifs rapportés a diminué dans les hôpitaux en Flandre Orientale (extinction de situations épidémiques), a augmenté dans la province d’Anvers et en région Bruxelloise et est resté stable en province de Liège.
Epidemiology of CR K. pneumoniae in oncology patients in Hacettepe

- June 2009-December 2010
- Active surveillance in neutropenic patients
- 43,312 rectal swabs
  - 100 colonized patients
  - 9 were infected with CRKP
- Records available for 93 patients colonized
  - 55.4 % immunosuppressed
  - 40 % hospitalized during the past 6 months
  - All had antibiotics during past month
  - 32.3 % died
- Beta-lactamases in 50 isolates
  - 38 OXA-48 and 39 CTX-M producers

Eser O et al, ECCMID 2013, Berlin
Clinical study on carbapenem sensitive & carbapenem resistant bacteremia in neutropenic & non-neutropenic patients-
The first series from India

Clinical outcome among neutropenic group

<table>
<thead>
<tr>
<th></th>
<th>Stable/discharged</th>
<th>Death</th>
<th>Not followed</th>
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<tr>
<td>Resistant neutropenic</td>
<td>8</td>
<td>9</td>
<td></td>
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<tr>
<td>Sensitive neutropenic</td>
<td>30</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

30 day mortality

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Resistant neutropenic</td>
<td>(52.94%)</td>
</tr>
<tr>
<td>Sensitive neutropenic</td>
<td>(30.23%)</td>
</tr>
</tbody>
</table>

Mortality p value

- < 0.001

Abdul Ghafur et al, ECCMID poster N°P1368, Berlin 2013
Distribution of etiologic agent isolated from bacteremia in patients with cancer in published studies since 2008

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</tr>
<tr>
<td>Gram negative</td>
<td>41 %</td>
<td>57.3 %</td>
<td>46.9 %</td>
<td>48.1 %</td>
<td>55.6 %</td>
<td>49 %</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
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<td>NS</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Gram positive</td>
<td>54 %</td>
<td>33.6 %</td>
<td>53.1 %</td>
<td>45.5 %</td>
<td>32.7 %</td>
<td>41 %</td>
</tr>
<tr>
<td><em>Staphylococcus spp.</em></td>
<td>55.2 %</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>9.5 %</td>
<td>NS</td>
<td>6.9 %</td>
<td>1.3 %</td>
<td>9.8 %</td>
<td>12 %</td>
</tr>
<tr>
<td><em>Coagulase-negative staph.</em></td>
<td>NS</td>
<td>NS</td>
<td>14.7 %</td>
<td>23.1 %</td>
<td>8.3 %</td>
<td>43 %</td>
</tr>
<tr>
<td><em>Enterococcus spp.</em></td>
<td>5.1 %</td>
<td>NS</td>
<td>9.5 %</td>
<td>5.8 %</td>
<td>9.2 %</td>
<td>23 %</td>
</tr>
<tr>
<td><em>Streptococcus spp.</em></td>
<td>5.5 %</td>
<td>NS</td>
<td>NS</td>
<td>6.4 %</td>
<td>3.4 %</td>
<td>NS</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>3.5 %</td>
<td>NS</td>
<td>2.3 %</td>
<td>NS</td>
<td>2 %</td>
<td>6 %</td>
</tr>
<tr>
<td><em>Streptococcus viridans</em></td>
<td>NS</td>
<td>NS</td>
<td>14 %</td>
<td>5.8 %</td>
<td>NS</td>
<td>23 %</td>
</tr>
</tbody>
</table>
Figure 3.15. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2013.
Pseudomonas aeruginosa bacteremia among hematological patients

- 441 cases (2004-2010)
- 66 due to P. aeruginosa
- 22 (33%) due to MDR strains
- Mortality
  - Higher in MDR strains (37% vs 23%, P=0.26)
  - Higher if inadequate empiric therapy (83% vs 18.8%, P=0.01)

# Results of Multiple logistic regression analysis using control group 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate P value</th>
<th>Multivariate</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P value</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Carbapenem use ≥7 defined daily dose</td>
<td>&lt; 0.001</td>
<td>0.001</td>
<td>23.8</td>
<td>3.5-166.67</td>
</tr>
<tr>
<td>History of previous P. aeruginosa infection</td>
<td>&lt; 0.001</td>
<td>0.12</td>
<td>13.7</td>
<td>1.79-111.1</td>
</tr>
<tr>
<td>Steroid use during prior 30 days</td>
<td>0.007</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>0.04</td>
<td>0.0033</td>
<td>25.0</td>
<td>1.30-480.90</td>
</tr>
<tr>
<td>Leukemia</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ohmagari N et al; Cancer 2005;104:205-212
ESKAPE pathogens isolated in 1148 bacteremias in cancer patients (2006-2011)

<table>
<thead>
<tr>
<th>Organism</th>
<th>ESKAPE N=382</th>
<th>rESKAPE N=54 (14.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus faecium</td>
<td>44</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>93</td>
<td>13 (24)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>95</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Actinetobacter baumanii</td>
<td>7 (1.8%)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>106</td>
<td>18 (33)</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>47</td>
<td>12 (22)</td>
</tr>
</tbody>
</table>

Carratala J, ECCMID 2013 Berlin
Resistance patterns in P. aeruginosa and Acinetobacter spp in cancer patients

Kara ö, ICAAC 2010, Boston, USA
S. maltophilia

- Incidence very low but increased in some institutions
- Prolonged neutropenia
- Exposure to broad-spectrum antibiotics: selective pressure by carbapenems
- Mechanical ventilation
- TMP-SMZ: increase of resistance

Safdar A; Clin Infect Dis 2007;45 (12):1602-1609.
### Addition of an anti-gram-positive (anti-GP) antibiotic to standard empirical antibiotics vs standard empirical antibiotics for cancer and febrile neutropenia

<table>
<thead>
<tr>
<th>Outcome at 30 days</th>
<th>Number of trials</th>
<th>Weighted event rates</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Empirical with anti-GP</td>
<td>Empirical without anti-GP</td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td>7 (852)</td>
<td>10%</td>
<td>12%</td>
<td>18% (-20 to 44)</td>
</tr>
<tr>
<td>Treatment failure (treatment modification counted)</td>
<td>10 (1779)</td>
<td>33%</td>
<td>44%</td>
<td>24% (15 to 32)</td>
</tr>
<tr>
<td>Overall treatment failure (treatment modification ignored)</td>
<td>6 (943)</td>
<td>19%</td>
<td>19%</td>
<td>0% (-27 to 21)</td>
</tr>
<tr>
<td>GP superinfection</td>
<td>9 (1688)</td>
<td>2.1%</td>
<td>8.1%</td>
<td>76% (60 to 86)</td>
</tr>
</tbody>
</table>

The addition of an anti-GP antibiotic should not be part of the initial empirical treatment of febrile neutropenia in patients with cancer (AI)

Borok et al, ACP Journal Club 2006;144:3
Addition of vancomycin to the initial regimen (IV)

CNS, Enterococci, Corynebacterium JK
- More indolent
- Few days delay not detrimental

Viridans streptococci, pneumococci and S. aureus:
- More fulminant

Risk for MRSA is determinant
- Patient previously colonized
- MRSA endemic in the unit
- Periporth cellulitis
- Furunculosis, folliculitis
- Breakthrough sepsis
Viridans group streptococci (VGS)

- Shock syndrome/ARDS: 7 - 39 %
- Mortality: 2 – 21 %
- Remain susceptible to cefepime and Pip/Tz. A small proportion R to carbapenem
- S. mitis
  - Most constantly Pen-R: 50 – 86 %
  - More prevalent in children (Bruckner L; Semin Pediatr Infect Dis 2006;17:153-160)
  - Most commonly associated with VGSS/ARDS (Bruckner L; Semin Pediatr Infect Dis 2006;17:153-160)
Viridans group streptococci

- 569 cases (2000 – 2010)
- Factors associated with Pen-R (MIC ≥ 2 µg/ml)
  - β-lactam use within 30 d
  - β-lactam prophylaxis
  - In patient at onset of FN
- Patients lacking 3 criteria: 1% of Pen-R
  PPV: 34%

MRSA

- Considerable geographic variation
- Widespread presence in hospital and community setting
- Europe: 43% of S. aureus isolates from blood are methicillin-resistant
- Neutropenic patients: 56% of S. aureus blood isolates were MRSA

14 centers – 8 countries – 2000’s (range 18 – 100 %) 
(Mikulska M et al, J Infect 2014;68:321-331)

- Vancomycin MIC ≥ 2µg/ml (54%)
  Higher failure rate
VRE in allo-HSCT

- MSKCC (2008-2009)
- 247 pts allo-HSCT
  - 43 pts with bacteremia < 30 days post transplant
  - 23 (53.5 %) due to VRE within 10 days post transplant
  - 13 (57 %) colonized on pretransplant screening

Risk factors
- VRE colonisation OR 3.88 (95% CI : 1.5-10.4; P=0.005)
- T cell depletion OR 10.89 (95% CI : 1.30-91.35; P=0.028)

Attributable mortality : 9 %

Kamboj M et al, Biol Blood Marrow Transplant 2010;16:1576-1581
### Implications for outcome

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MDRGNB, N=51 n (%)</th>
<th>Non-MDRGNB, N=312 n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate initial empirical antibiotic therapy</td>
<td>35 (69)</td>
<td>29 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to adequate antibiotic therapy &gt;48h</td>
<td>21 (41)</td>
<td>13 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU admission</td>
<td>7 (14)</td>
<td>14 (4)</td>
<td>0.023</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>7 (14)</td>
<td>10 (3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Early case fatality rate (7 days)</td>
<td>9 (18)</td>
<td>33 (11)</td>
<td>0.15</td>
</tr>
<tr>
<td>Overall case-mortality rate (30 days)</td>
<td>20 (39)</td>
<td>62 (20)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Risk factors for antibiotic resistant bacteremia in neutropenic patients

1. Colonization
   • Stool:
     • ESBL (RR 4.5, 95% CI 2.89-7.04)
     • VRE (RR 10.2, 95% CI 7.87-13.32)
   • Nares, skin:
     • MRSA

2. Exposure to broad spectrum antibiotics
   • ESBL:
     • Prior fluoroquinolones
     • Prior use of third generation cephalosporins
   • P. aeruginosa, S. maltophilia
     • Prior use of carbapenems

3. Severe illness:
   • AML
   • Comorbidities

4. Urinary catheter

Three-drug therapy for bloodstream infections from carbapenemase-producing Klebsiella pneumoniae

- Klebsiella bacteraemia 125 cases-retrospective analysis
- 60% of the empirical regimens to be inadequate
- Forty-six patients (37%) received monotherapy; 79 (63%) received two or more antibiotics
- 30 days mortality rate was significantly higher among monotherapy recipients than among combination therapy recipients (54% vs. 34%)
- Mortality was lowest (13%) for patients who received combination therapy with colistin, tigecycline, and meropenem (P=0.01)

Tumbarello M et al, CID 2012;5:943
Efficacy of antimicrobial regimens for carbapenemase-producing *K.pneumoniae* infections

<table>
<thead>
<tr>
<th>Antibiotic regimen</th>
<th>Nº of patients</th>
<th>Outcome success (%)</th>
<th>Failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotic regimen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td>64 (24.2)</td>
<td>35 (54.7)</td>
<td>29 (45.3)</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>8 (4.7)</td>
<td>5 (62.5)</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>16 (6.8)</td>
<td>12 (75.0)</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>23 (9.8)</td>
<td>18 (78.3)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>111 (47.5)</td>
<td>70 (63.1)</td>
<td>41 (36.9)</td>
</tr>
</tbody>
</table>

| Combination therapy                     |                |                     |             |
| Two or more active drugs (carbapenem not included) | 52 (22.2)      | 38 (73.1)           | 14 (26.9)   |
| Two or more active drugs (carbapenem included) | 30 (12.8)      | 28 (93.3)           | 2 (6.7)     |
| **Total**                                | 82 (35.0)      | 66 (80.5)           | 16 (19.5)   |
| ‘inappropriate’ therapy                  | 41 (17.5)      | 23 (56.1)           | 18 (43.9)   |
| **Total**                                | 234 (100)      | 159 (67.9)          | 75 (32.1)   |

Akova M et al; Clin Microbiol Infect 2012; 18,439
Anti-anaerobic coverage mandatory (IV)

- Severe mucositis
- Typhlitis
- Perianal abscess
- Allogeneic BMT

Lark LB, Clin Inf Dis 2001;33:338-343
Fanourgiakis P, Suppot Care Cancer 2003;11:332-335
Monotherapy versus combination therapy

Two metaanalysis:
- Furno, Lancet ID 2002; vol 2 issue 4: 231-242
- Paul, BMJ 2003; vol 326

→ no advantage (AI)
Mortality

<table>
<thead>
<tr>
<th></th>
<th>Sepsis on admission</th>
<th>Breakthrough sepsis</th>
<th>No sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nb of pts</td>
<td>27</td>
<td>75</td>
<td>919</td>
</tr>
<tr>
<td>Death</td>
<td>5 (18.5 %)</td>
<td>31 (41.3 %)</td>
<td>20 (2.2 %)</td>
</tr>
</tbody>
</table>
Combination therapy β-lactam + aminoglycoside

- Double coverage
- Therapeutic synergy
- Prevention of emergence of resistance
- Risk of nephrotoxicity
Combination therapy β-lactam + aminoglycoside for 3 days (IV)

- Patient with sepsis or septic shock
  AND
- Patient at high risk of *P. aeruginosa* or GNB bacteremia
Modification of initial therapy in pts with persisting fever

- Patient hemodynamically stable:
  - Wait until day 5 (Cometta, Clin Infect Dis 2003;37:382-389)
  - After day 5:
    - Shift to carbapenem (Kliasova, Abstract, Febrile Neutropenia 1997)
    - Perform chest and sinus CT scan
    - Galactomannan test
    - Add empiric antifungal?
    - Work-up for viral (CMV, EBV, HHV6, ...) and parasitic infection

- Patient deteriorating:
  - Hypotension
  - Tachypnea, tachycardia
  - Tissue hypoperfusion
  - Shift to carbapenem
  - Add glycopeptide
  - Add antifungal
INSTITUTION RELATED

- % susceptibility of P. aeruginosa
- Incidence of GN-ESBL+
- MRSA endemity
- % S. viridans pen-R

PATIENT-RELATED

- Risk category
- Primary or secondary episode
- previous AB used
- Previous fluoroquinolone prophylaxis
- Colonisation by MRSA, VRE
- Signs of sepsis
- Specific site of infection or FUO
- Allergy to ABS or renal or hepatic insufficiency

Empiric therapy choices:
- oral or IV?
- β-lactam monotherapy?
- Combination of β-lactam
  - With aminoglycoside?
  - With glycopeptide?
- Initial anti-anaerobic coverage?
Is there a difference between 1st line molecules

Ceftazidime
Cefepime
Piperacillin/tazobactam
Shift towards Gram-positive
- Cefepime and pip/tazo more active on Streptococcus viridans and Staphylococcus aureus
  (Elting, Clin Inf Dis 1997;25:247-259)
- Less need for glycopeptide
  (Owens, Clin Inf Dis 2000;31:291)
- Emergence of ESBLs
  (Paterson, Clin Inf Dis 2004;38:S341-S345)
  (Johnson, J Inf Dis 1990;162:981-983)
Clinical evidence of monotherapy for primary episodes of febrile neutropenia in high-risk patients

- Meropenem
- Imipenem: (AI)
  - Relevance (epidemiology): good
  - Relevance (population): good
- Piperacillin/tazobactam: (AI)
  - Relevance (epidemiology): moderate
  - Relevance (population): good
- Cefepime: (AI)
  - Relevance (epidemiology): moderate
  - Relevance (population): good
Clinical evidence of monotherapy for primary episodes of febrile neutropenia in high-risk patients

- Ceftazidime: (AI)
  Relevance (epidemiology): poor
  Relevance (population): good

- Aztreonam: (+glycopeptide)
  (AI)
  Relevance (epidemiology): poor
  Relevance (population): poor
  Reserved to patients allergic to β-lactams
### New antimicrobials in development against GNB

<table>
<thead>
<tr>
<th>Product</th>
<th>Antimicrobial class</th>
<th>Trial status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avibactam</td>
<td>ß-lactamase inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Ceftaroline/avibactam</td>
<td>ß-lactamase inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Ceftazidime/avibactam</td>
<td>ß-lactamase inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Imipenem/MK-7655</td>
<td>ß-lactamase inhibitor</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>Aminoglycoside</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Eravacycline</td>
<td>Fluorocycline</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Brilacidin</td>
<td>Peptide mimetic</td>
<td>Phase 2</td>
</tr>
<tr>
<td>ACHN-975</td>
<td>LPX-C inhibitor</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Anti-Pseudomonas</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

- **Avibactam**: Broadest activity of ß-lactamase inhibitors - Active against ESBL (CTX-M15, AmpC) and KPC - Not against OXA-48, NDM-1
- **Plazomicin (phase 3)**: Next generation aminoglycoside - Retains potent activity against aminoglycoside and carbapenem-resistant strains
- **Imipenem/MK-7655**: Inhibition of KPC - Less active against OXA-48 - No activity against MBL(s) - Increases the activity of imipenem against P. aeruginosa in general and OprD mutant
- **Eravacycline**: Fluorocycline - ≥ 2 fold lower MIC(s)
- **Brilacidin**: Peptide mimetic - Defensin mimetic acts by disrupting bacterial membrane - Activity against GP and GN - Active against ESBL and NDM-1 Pseudomonas - No activity against Acinetobacter
- **ACHN-975**: Inhibitor of LPX-C - Potent activity against P. aeruginosa - No preexisting resistance - Potent activity against P. aeruginosa - No preexisting resistance
In Conclusion

- Continuously and rapidly changing epidemiology
- Increase of GNB resistance is a major challenge for empiric therapy
- Better define risk factors of MDR
- Control measures
  - Hand hygiene
  - Limit underdosing and use of carbapenems
  - Antibiotic stewardship
  - Surveillance cultures
New Approach
Risk adapted strategy

• Accurate selection of patients at low-risk
• Oral antibiotics
• Out patient management
Score derived from the logistic equation of the MASCC predictive model
(1386 PATIENTS WITH FEBRILE NEUTROPENIA)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burden of illness</td>
<td></td>
</tr>
<tr>
<td>• No or mild symptoms</td>
<td>5</td>
</tr>
<tr>
<td>• Moderate symptoms</td>
<td>3</td>
</tr>
<tr>
<td>No hypotension</td>
<td>5</td>
</tr>
<tr>
<td>No chronic obstructive pulmonary disease</td>
<td>4</td>
</tr>
<tr>
<td>Solid tumor or no previous fungal infection in hematological ca</td>
<td>4</td>
</tr>
<tr>
<td>Outpatient status</td>
<td>3</td>
</tr>
<tr>
<td>No dehydration</td>
<td>3</td>
</tr>
<tr>
<td>Age &lt; 60 years</td>
<td>2</td>
</tr>
</tbody>
</table>

Threshold: score ≥ 21 (maximum 26) predicting less than 5% of severe complications

J. Klastersky et al. (2001)
Flow-chart of study design
(unicentric study - Institut Jules Bordet)

Mascc risk-index score assessment

< 21 or ≥ 21
and not eligible for oral trt

Hospitalisation and IV treatment
(piperacillin-tazobactam)

Follow-up only

≥ 21
and eligible for oral trt

Oral treatment and treatment for 24 hours

Early discharge if patient is stable and willing to go back home with daily phone contact

Follow-up only
Proportion of 3rd gen. cephalosporins Resistant (R) Escherichia coli Isolates in Participating Countries

2007

2013
Proportion of 3rd gen. cephalosporins Resistant (R) Klebsiella pneumoniae Isolates in Participating Countries

2007

2013
Sites of infection among infectious febrile episodes in neutropenics (n=80)

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Episodes</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORL</td>
<td>17</td>
<td>21.3%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>12</td>
<td>15.0%</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>6</td>
<td>7.5%</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>6</td>
<td>7.5%</td>
</tr>
<tr>
<td>Neurological</td>
<td>2</td>
<td>2.5%</td>
</tr>
<tr>
<td>Soft tissues</td>
<td>5</td>
<td>6.3%</td>
</tr>
<tr>
<td>Septic shock</td>
<td>5</td>
<td>6.3%</td>
</tr>
<tr>
<td>Primary bactereamia</td>
<td>15</td>
<td>18.8%</td>
</tr>
<tr>
<td>Secondary bactereamia</td>
<td>11</td>
<td>13.8%</td>
</tr>
<tr>
<td>other</td>
<td>1</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

From Toussaint et al, Supp Care in Cancer 2006