Approaches to febrile neutropenia

2011 IDSA-ECIL guidelines

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Febrile Neutropenia: Definition

• Definitions are not hard-and-fast rules

• **Fever** is a single **oral** temperature measurement of ≥38.3°C or a temperature of ≥38.0°C sustained for a 1-h period
  – Axillary temperature is discouraged
  – Rectal temperature measurements should be avoided

• **Neutropenia** is defined as an ANC of < 500 cells/mm³ or an ANC that is expected to decrease to < 500 cells/mm³ during the next 48 hours
  – “functional neutropenia” patients are also at risk

• **Non-infectious causes** of fever should be excluded: transfusion of blood products; chemotherapeutic agents; tumor lysis syndrome; diffuse intravascular coagulation; cerebral lesions; graft-versus-host disease; drug-fever. Beware of corticosteroids!
Frequency of Infectious Agents in Neutropenic Cancer Patients

- **Bacteria**: 70 - 90%
- **Fungi**: 5 - 20%
- **Viruses**: 2 - 5%
- **Parasites**: < 1 %
Evolution of the Mortality due to Bacterial Infections in Neutropenic Cancer Patients
IDSA-ECIL 2011 Recommendations

1. Risk assessment and low-risk versus high risk
2. Specific tests and cultures
3. What empirical antibiotic therapy and in what setting?
4. Modification: when en how?
5. How long?
6. When should antibiotic prophylaxis be given?
7. Empirical antifungal therapy
8. Antifungal prophylaxis or preemptive therapy
9. Antiviral prophylaxis
10. Role of hematopoietic growth factors
11. Management of catheter-related infections
12. Environmental precautions

1. Risk assessment

What distinguishes high-risk and low-risk patients
<table>
<thead>
<tr>
<th>Type of chemotherapy</th>
<th>LOW</th>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>« Standard » chemotherapy for solid tumor, lymphoma, myeloma</td>
<td>« Standard » chemotherapy for solid tumor, lymphoma, myeloma</td>
<td>Induction / consolidation chemotherapy for acute leukemia autologous or allogeneic HSCT</td>
</tr>
<tr>
<td>Disruption of mucous Membranes</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Duration of profound neutropenia &lt; 0.1 G/L</td>
<td>≤ 7 days</td>
<td>≥ 7 days</td>
</tr>
<tr>
<td>FEBRILE NEUTROPENIA</td>
<td>5 – 20 %</td>
<td>80 – 100%</td>
</tr>
</tbody>
</table>
Etiology of Febrile Neutropenia

Low Incidence of FN

- Bacteremia: 5-10%
- Other MDI: 5-10%
- Clinically documented: 10-20%
- FUO: 60-70%

High Incidence of FN

- Bacteremia: 25-35%
- Other MDI: 5-10%
- Clinically documented: 10-20%
- FUO: 40-50%
The MASCC Risk Index for Prediction of the Absence of Serious Complications

*Klustersky et al., J Clin Oncol, 2000; 18: 3038-51*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burden of illness: no or mild</td>
<td>5</td>
</tr>
<tr>
<td>moderate</td>
<td>3</td>
</tr>
<tr>
<td>No hypotension</td>
<td>5</td>
</tr>
<tr>
<td>No COPD</td>
<td>4</td>
</tr>
<tr>
<td>Solid tumor or no previous fungal infection</td>
<td>4</td>
</tr>
<tr>
<td>No dehydration</td>
<td>3</td>
</tr>
<tr>
<td>Outpatient status</td>
<td>3</td>
</tr>
<tr>
<td>Age &lt; 60 years</td>
<td>2</td>
</tr>
</tbody>
</table>

Maximum score 26
1. IDSA-ECIL 2011 Definition of High-Risk Patients

- MASCC score < 21
- Profound neutropenia (ANC ≤ 100 cells/mm$^3$) anticipated to extend > 7 days
- Presence of any co-morbid medical problem including but not limited to:
  - Hemodynamic instability
  - Oral of GI mucositis that interferes with swallowing or causes severe diarrhea
  - GI symptoms, including abdominal pain, nausea and vomiting, or diarrhea
  - Neurologic or mental status changes of new onset
  - Intravascular catheter infection, especially catheter tunnel infection
  - New pulmonary infiltrate or hypoxemia, or underlying chronic lung disease
- Evidence of hepatic insufficiency
  - Aminotransferase levels > 5 x ULN
- Evidence of renal insufficiency
  - Creatinine clearance of < 30 mL/min

These patients should initially receive IV empirical antibiotic therapy in the hospital (B-I)
2. When should Antibiotic Prophylaxis be given, and with what Agents
Meta-Analyses of First-Generation Fluoroquinolone (FQ) Prophylaxis vs. Placebo/No Prophylaxis

ENDPOINT: GRAM-NEGATIVE BACTEREMIA

Relative risk (95%CI)

- **Cruciani, Clin Infect Dis, 1996**
  - 13 trials 1986 – 1994: n=1155
  - 0.09 (0.05-0.16)

- **Engels, J Clin Oncol, 1998**
  - 6 trials 1987 – 1993: n=731
  - 0.23 (0.11-0.49)

- **Van de Wetering, Eur J Cancer, 2005**
  - 5 trials 1986 – 2001: n=466
  - 0.16 (0.07-0.39)

- **Gafter-Gvili, Ann Intern Med, 2005**
  - 18 trials 1980 – 2002: n=1407
  - 0.26 (0.20-0.35)
Meta-Analyses of First-Generation Fluoroquinolone Prophylaxis vs. Placebo or No Prophylaxis

ENDPOINT: INFECTION-RELATED MORTALITY

Relative risk (95%CI)

Cruciani, Clin Infect Dis, 1996
13 trials 1986 – 1994: n=1155
0.79 (0.47-1.34)

Engels, J Clin Oncol, 1998
5 trials 1987 – 1993: n=731
1.04 (0.4-2.7)

Van de Wetering, Eur J Cancer, 2005
6 trials 1986 – 2002: n=561
0.43 (0.15-1.27)

Gafter-Gvili, Ann Intern Med, 2005
10 trials 1980 – 2002: n=1022
0.38 (0.21-0.69)
## Evolution of Resistance and Fluoroquinolone Prophylaxis
### EORTC-IATG Trials


**EORTC-IATG Database**

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of patients</th>
<th>FQ-prophylaxis</th>
<th>Gram-negative bacteremia</th>
<th>FQ-resistant <em>E. coli</em> bacteremia</th>
<th>Infectious mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983-1985</td>
<td>219</td>
<td>1%</td>
<td>12%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>1991-1993</td>
<td>706</td>
<td>45%</td>
<td>8%</td>
<td>28%</td>
<td>1%</td>
</tr>
<tr>
<td>1997-2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- FQ-prophylaxis: 1991-1993 compared to 1983-1985 increased by 44%.
- FQ-resistant *E. coli* bacteremia: 1991-1993 compared to 1983-1985 increased by 28%.
- Infectious mortality: 1991-1993 compared to 1983-1985 decreased by 1%. 

**Note:** The data for 1997-2000 is not provided in the table.
2. IDSA-ECIL Recommendations on Prophylaxis

• FQ prophylaxis should be considered for high-risk patients with expected durations of prolonged and profound neutropenia (IDSA B-I)
  – Levofloxacin
  – Ciprofloxacin
  – European guidelines: A-I

• A systematic strategy for monitoring the development of FQ resistance among gram-negative bacilli is recommended (A-II)

• Addition of a gram-positive active agent to FQ prophylaxis is not recommended (A-I).

• Antibacterial prophylaxis is not routinely recommended for low-risk patients who are anticipated to remain neutropenic for < 7 days (A-III)
3. What Empiric Antibiotic therapy is Appropriate and in what Venue
Empirical Antibiotic Therapy in Granulocytopenic Cancer Patients


*Pseudomonas aeruginosa* bacteremia

1968-69: **Combination** carbenicillin + gentamycin started *after* results of blood cultures

MORTALITY 50%

1970-71: Same antibiotics started *with development of fever*

MORTALITY 26%
IMMEDIATE EMPIRICAL COMBINATION ANTIBIOTIC THERAPY (anti-Pseudomonal penicillin + aminoglycoside) AT ONSET OF FEVER is the CORNERSTONE of management of neutropenic cancer patients.
MONOTHERAPY with bactericidal broad-spectrum beta-lactam antibiotics IS AS AFFECTIVE AS the COMBINATION of beta-lactam + aminoglycoside
First-Line Use of Vancomycin for the Empirical Treatment of Febrile Neutropenic Patients?

Not recommended (A-I)

EORTC-IATCG, J Infect Dis, 1991; 163: 951-8
Second-Line Use of Empirical Vancomycin for Persistent Fever (>72h) in Neutropenic Cancer Patients?

*Cometta et al. for the EORTC-IATG, Clin Infect Dis, 2002; 37: 382-9*
Febrile neutropenia in high-risk patients (IDSA)

Anti-pseudomonal Penicillin + Beta-lactamase Inhibitor (A-I)  

or

Carbapenem (A-I)  

or

(3\textsuperscript{rd}- or 4\textsuperscript{th}-Generation Cephalosporin (A-I)

+ Aminoglycoside or FQ (B-III)

If:  
- Severe sepsis or septic shock  
- High incidence or suspicion of infection with \textit{P. aeruginosa} or resistant Gram-negative bacteria  
- Pneumonia

+ Glycopeptide (B-III)

If:  
- Severe sepsis or septic shock  
- Intravascular catheter-related infection  
- High incidence or suspicion of infection with resistant Gram-positive bacteria  
- Skin or soft-tissue infection/pneumonia
Empirical therapy for febrile neutropenia
Escalation vs. De-escalation approach (ECIL)

- **Escalation**: initial antibacterial regimen targeted to the more frequent bacteria identified in a given centre, then an adaptation of that regimen in a given patient, 24-72 h later, once a pathogen is known.

- **De-escalation**: initial broad-spectrum empirical therapy talking into account the worst expected scenario of resistant bacteria in a given centre. 24-72 h later, the antibacterial therapy should be stepped down when possible according to the clinical course and the microbiological results.
ECIL 4 guidelines: Approach to initial regimens in escalation and de-escalation approaches

- **Escalation**
  - 4th generation cephalosporin
  - Piperacillin-tazobactam
  - No anti-resistant Gram-positive coverage
  - No combination with aminoglycosides/quinolones

- **De-escalation**
  - Carbapenem
  - Combination beta-lactam with aminoglycoside or quinolones
  - Combination beta-lactam with colistin
  - Early anti-resistant Gram-positive coverage with vancomycin or a new anti-Gram positive agent