Febrile Neutropenia: Guideline Review
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Objectives

- Recall common pathogens that cause neutropenic fever
- Define terms related to neutropenic fever
- Stratify patients at risk for neutropenia
- Identify appropriate empiric antimicrobial treatments for neutropenic fever based on patient-specific factors

Epidemiology of Febrile Neutropenia

- Frequency of fever during ≥1 chemotherapeutic cycle
  - Solid tumors: 10-50% of patients
  - Hematologic malignancy: >80% of patients
- Patient population may not show characteristic signs/symptoms of infection
  - Clinically documented infection happens 20-30% of the time
- A medical emergency
  - Up to 70% mortality if initiation of antibiotics delayed
  - Progression of illness may be rapid
Common Bacterial Pathogens

<table>
<thead>
<tr>
<th>Gram-positive</th>
<th>Gram-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase (-) Staphylococcus</td>
<td>E. coli</td>
</tr>
<tr>
<td>S. aureus</td>
<td>Klebsiella spp.</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>Enterobacter spp.</td>
</tr>
<tr>
<td>Viridans streptococci</td>
<td>P. aeruginosa</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>Citrobacter spp.</td>
</tr>
<tr>
<td>S. pyogenes</td>
<td>Acinetobacter spp.</td>
</tr>
<tr>
<td></td>
<td>Stenotrophomonas maltophilia</td>
</tr>
</tbody>
</table>


Bacterial Pathogens

<table>
<thead>
<tr>
<th>Year</th>
<th>Gram (+)</th>
<th>Gram (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973-76</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>1980-83</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>1986-88</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>1993-94</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>2000</td>
<td>30%</td>
<td>70%</td>
</tr>
</tbody>
</table>


Common Fungal & Viral Pathogens

<table>
<thead>
<tr>
<th>Fungi</th>
<th>Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida spp.</td>
<td>Herpes simplex</td>
</tr>
<tr>
<td>Aspergillus spp.</td>
<td>Varicella zoster</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus</td>
</tr>
</tbody>
</table>

Patient Work-Up

- Physical examination: potential sites of infection
- Laboratory and other tests:
  - Hematology: CBC with differential
  - Chemistry: SCr, BUN, electrolytes, total bilirubin, transaminases
  - Microbiology: collect cultures prior to initiating antimicrobials
    - Blood cultures (2 sets)
    - Culture other sites per clinical signs and symptoms
  - Radiology per clinical signs and symptoms

Review of the Immune System

- 1st line of defense: Physical barriers
  - Skin and mucosa

- 2nd line: Innate immune system (immediate)
  - Neutrophils, macrophages, complement, and NK cells

- 3rd line: Adaptive immune system
  - Production of antibodies & memory cells

Components of the Immune System
Neutropenia

- Absolute neutrophil count (ANC) < 500 cells/mm³ OR < 1,000 cells/mm³ with a predicted decrease to < 500 cells/mm³ during the next 48 hours

\[
\text{ANC} = \frac{\text{(WBC)} \times (\%\text{Segs} + \%\text{Bands})}{100}
\]

- Increased susceptibility to infection begins at < 1000 cells/mm³
  - Severe risk with ANC < 100 cells/mm³

Frequency and severity of infections
Inverse proportion
Neutrophil Count

\[\text{ANC cells/mm³} \quad \text{Infections per 100 days}\]

ANC Risk Relation

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Allison C. Friell,¹ Eric J. Bown¹ Kent A. Sopko² Michael J. Boeckh,² James I. Ina³ Craig A. Mullen,² Ioan I. Raul,³ Kenneth K. Relihan,⁴ Jo-Aimee H. Young,⁵ and John R. Wiegand²
Patient Case: Mrs. Smith- Day 1

- Diagnosed with acute myelogenous leukemia
- Completed induction chemotherapy and awaiting neutrophil recovery
- PMH: Hypertension
- Serology studies: HSV seropositive, VZV seronegative
- She has no known drug allergies

ANC Calculation

<table>
<thead>
<tr>
<th>Result Name</th>
<th>Result</th>
<th>Abnl</th>
<th>Normal Range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>1.4</td>
<td>L</td>
<td>4.0-10.0</td>
<td>X1000</td>
</tr>
<tr>
<td>HGB</td>
<td>110</td>
<td>L</td>
<td>12.0-16.0</td>
<td>G/DL</td>
</tr>
<tr>
<td>HCT</td>
<td>35.0</td>
<td>L</td>
<td>37.0-47.0</td>
<td>%</td>
</tr>
<tr>
<td>MCV</td>
<td>82.3</td>
<td>M</td>
<td>77.0-94.0</td>
<td>FL</td>
</tr>
<tr>
<td>MCH</td>
<td>27.0</td>
<td>M</td>
<td>26.0-31.0</td>
<td>PG</td>
</tr>
<tr>
<td>RDW</td>
<td>13.1</td>
<td>M</td>
<td>11.5-14.5</td>
<td>G/DL</td>
</tr>
<tr>
<td>PLT</td>
<td>133</td>
<td>M</td>
<td>100-300</td>
<td>X1000</td>
</tr>
</tbody>
</table>

PROPHYLAXIS
**Prophylactic Antimicrobials**

- **Indications**
  - Expectation of prolonged and profound neutropenia
    - $\leq 100$ cells/mm$^3$ for $>7$ days
- **Desired properties**
  - Favorable side effect profile
  - Few drug interactions
  - Easy to administer (QD or Q12h dosing)
  - PO and IV formulations (necessary if mucositis occurs)


**Prophylactic Antibiotics**

- **Fluoroquinolones (FQs)**
  - Levofloxacin (preferred)
  - Ciprofloxacin
- **Clinical evidence**
  - Significant reduction in:
    - Number of febrile episodes
    - Documented infections
    - Blood stream infections
    - Single-agent gram (-) blood stream infections
  - Concerns include side effects, resistance, and lack of gram (+) coverage


**Candida Prophylaxis**

- **High risk patients**
  - Allogeneic HSCT
  - Post-chemotherapy neutropenic AML patients
  - History of *Candida* infection during prior episode of neutropenia
- **Antifungal of choice**
  - Fluconazole
- **Alternatives**
  - Itraconazole
  - Posaconazole
  - Voriconazole
  - Micafungin
  - Caspofungin
  - Anidulafungin

Aspergillus Prophylaxis

- High risk patients
  - Undergoing high intensity chemotherapy for AML or MDS
- Antifungal of choice
  - Posaconazole
- HSCT
  - Risk for GVHD
  - Prior invasive aspergillosis
  - Anticipated prolonged neutropenia (>2wks)
  - Prolonged neutropenia prior to HSCT

HSV/VZV Prophylaxis

- Indications
  - High level of immunosuppression (acute leukemia)
  - History of HSV/VZV or seropositivity
  - Seronegative recipients with seropositive transplant donors
- Antiviral used: Acyclovir

Infection Prevention

- Hand washing
- Decreased number of venipunctures
- Neutropenic diet
- Environment
- Passive immunity (IVIG)
- Prophylactic antimicrobials
- Influenza vaccination
Mrs. Smith- Day 3

ANC has decreased to 0. In order to prevent neutropenic fever what antimicrobials should she be prescribed?

Neutropenic Fever

**Fever**
- Single oral temperature of $\geq 38.3^\circ C (101^\circ F)$
- Oral temperature of $\geq 38.0^\circ C (100.4^\circ F)$ sustained for 1 hr

**Neutropenia**
- Neutrophil count of <500 cells/mm$^3$
- Neutrophil count of <1000 cells/mm$^3$ with a *predicted* decrease to <500 cells/mm$^3$ over the next 48 hours

Risk Assessment

**Fever + Neutropenia**

**Low Risk**
- ALL of the following:
  - Anticipated neutropenia $\leq 7$ days
  - Clinically stable
  - No medical comorbidities
  - Stable and adequate hepatic and renal function

  OR

  MASCC Score $\geq 21$

**High Risk**
- ANY of the following:
  - Anticipated profound neutropenia (ANC$\leq 100$) $> 7$ days
  - Hemodynamically unstable
  - Any medical comorbidities
  - Hepatic insufficiency
  - Renal insufficiency

  OR

  MASCC Score $< 21$
Multinational Association for Supportive Care in Cancer (MASCC) 
Risk-Index Score

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burden of febrile neutropenia</td>
<td></td>
</tr>
<tr>
<td>Mild to absent symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>3</td>
</tr>
<tr>
<td>Severe symptoms or moribund</td>
<td>0</td>
</tr>
<tr>
<td>No hypotension (SBP &gt; 90 mmHg)</td>
<td>5</td>
</tr>
<tr>
<td>No COPD at onset of febrile episode</td>
<td>4</td>
</tr>
<tr>
<td>No previous fungal infection</td>
<td>4</td>
</tr>
<tr>
<td>No dehydration requiring parenteral fluids</td>
<td>3</td>
</tr>
<tr>
<td>Outpatient onset of febrile episode</td>
<td>3</td>
</tr>
<tr>
<td>Age &lt; 60 years</td>
<td>2</td>
</tr>
</tbody>
</table>

**Low risk**: risk index score ≥ 21

Empiric Antimicrobial Considerations

Drug allergies  
Renal/hepatic function  
Site of infection  
Risk of drug-resistant pathogens

Patient Specific Factors  
Bactericidal  
Anti-pseudomonal activity  
Etiology of infection  
Minimize toxicity  
Timely initiation

Institutional Factors

Antibiotic Regimen Factors  
Local resistance/susceptibility patterns

Initial Management: Low Risk

• Low risk
  – Outpatient
    • Oral regimen if able to tolerate and absorb  
    • Availability of caregiver, telephone, and transportation  
    • Preferred regimen
      – Ciprofloxacin + Amoxicillin/clavulanate  
      – Severe penicillin allergy: Ciprofloxacin + clindamycin
  – Inpatient IV
    • Documented infection requiring IV antibiotics  
    • GI intolerance  
    • Preferred regimen?
Initial Management: High Risk

Fever + Neutropenia

- Low Risk
- Outpatient Oral
  - Ciprofloxacin + Amoxicillin/clavulanate
- Inpatient IV
  - Empiric anti-pseudomonal β-lactam monotherapy
  - Piperacillin/tazobactam
  - Cefepime
  - Carbapenem
  - Penicillin allergy

Inpatient IV Antibiotics

- Inpatient IV Antibiotics
  - Empiric anti-pseudomonal β-lactam monotherapy
  - Piperacillin/tazobactam
  - Cefepime
  - Carbapenem
  - Penicillin allergy


Anti-pseudomonal β-lactams

<table>
<thead>
<tr>
<th>Activity</th>
<th>Piperacillin-tazobactam</th>
<th>Cefepime</th>
<th>Carbapenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>ESBL producer</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
</tr>
</tbody>
</table>

Ceftazidime:
- Poor activity against gram positive bacteria, notably viridans streptococci


Penicillin Allergy

- Delayed-type hypersensitivity reaction:
  - Definition: rash
  - Anti-pseudomonal cephalosporin
- Immediate-type hypersensitivity reaction:
  - Definition: hives or bronchospasm
  - Regimen: aztreonam + vancomycin

Mrs. Smith

- Day 5 of neutropenia
- VS: Tmax: 101.3; HR: 75; BP: 115/75; RR: 18; O₂: 99% on room air
- Blood cultures are drawn
- Asymptomatic aside from fever
- Physical exam yields no skin findings
- IV line sites look good

Mrs. Smith - Day 5

What is the next step in therapy management for her?

Initial Management: High Risk

Fever + Neutropenia

High Risk

Inpatient IV Antibiotics
Empiric anti-pseudomonal β-lactam monotherapy
- Piperacillin/tazobactam
- Cefepime
- Carbapenem
- Penicillin allergy

Need for Additional Therapy
- Pneumonia
- Skin & Soft Tissue infection
- Catheter-associated blood stream
- Abdominal infection

### Treatment of Drug-Resistant Gram-Positive Organisms

No longer a standard part of empirical antibiotic therapy for neutropenic fever

#### Indications for Empiric Addition of Antibiotics Active Against Gram-Positive Organisms

<table>
<thead>
<tr>
<th>Indication</th>
<th>Antibiotic(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamic instability</td>
<td>Suspected serious catheter-related infection</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Skin and soft tissue infection</td>
</tr>
<tr>
<td>Positive blood culture with gram-positive bacteria prior to final speciation and susceptibility testing</td>
<td>Colonization with MRSA, VRE, or penicillin-resistant <em>Streptococcus pneumoniae</em></td>
</tr>
</tbody>
</table>


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### Initial Management: High Risk

**Fever + Neutropenia**

**High Risk**

- **Inpatient IV Antibiotics**
  - Empiric anti-pseudomonal β-lactam monotherapy
  - Piperacillin/tazobactam
  - Cefepime
  - Carbapenem
  - Penicillin allergy

- **Need for Additional Therapy**
  - Pneumonia
  - Skin & Soft Tissue
  - Central line-associated blood stream infection
  - Abdominal

- **Need for Modifications to Therapy**
  - MRSA
  - VRE
  - ESBL producing gram negative
  - Carbapenemase producing

**Reassess after 2 – 4 days**

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### Continuing Therapy

**Day 2-4 after empiric antibiotics**

**Documented infection**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Clinically stable</td>
</tr>
<tr>
<td>No</td>
<td>Reassess sites/sources of infection</td>
</tr>
<tr>
<td>Yes</td>
<td>Broden antibiotics</td>
</tr>
<tr>
<td>No</td>
<td>Consider empiric antifungals (after 4-7 days)</td>
</tr>
</tbody>
</table>

**Target antibiotics**

- Continue for 7-14 days or until ANC >500 cells/mm³ and increasing

**Continue**

- until ANC >500 cells/mm³ and increasing

**Stop vancomycin if no gram positive infection identified at 2 days**

Prolonged Fever (>4 days)

Unexplained fever & clinically stable

With rising ANC
- Myeloid recovery imminent

Action
- Continue antibiotics and observe unless there is evidence of new infection

Without rising ANC
- Further evaluation for cause

Action(s)
1. Continue current antibiotic regimen
2. Change or add antibiotic(s)
3. Start antifungal therapy

Fungal Infections

Unexplained fever, clinically stable, myeloid recovery not imminent

Receiving anti-yeast prophylaxis
- Pre-emptive antifungal based on results of *CT scan
  *Serial serum galactomannan

Receiving anti-mold prophylaxis
- Empiric anti-mold coverage
  *Echinocandin
  *Amphotericin B

Consider switch to a different class of mold active agent
Fungal Infections

- Incidence ranges from 2–47%
  - Dependent on risk factors and cytotoxic therapy
- Mortality ~90% in invasive fungal infections in BMT patients
  - Aspergillosis
- Timeline of fungal infections
  - ≥ 1 week of neutropenia ➔ Candida
  - ≥ 10-15 days ➔ Aspergillus

Diagnostic Reassessment

- CT scan
  - Characterize bacterial or fungal processes
- Galactomannan
  - Component of Aspergillus cell wall
  - ELISA detects antigen in serum or bronchial washing
- β-(1,3) D-glucan
  - Component of Candida cell wall and many molds
**Candida Species**

- More than 150 Candida species
- ≈ 6 clinically significant human pathogens
  - **C. albicans**
  - **C. parapsilosis**
  - **C. tropicalis**
  - **C. glabrata**
  - **C. krusei**
  - **C. lusitaniae**

**Candida Spectrum of Infection**

- **Cutaneous fungemia**
- **Disseminated**
- **Mucosal**
- **Chorioretinitis**
Candidiasis

Risk factors in neutropenic patients
- Extended duration of neutropenia
- Mucosal disruption from cytotoxic chemotherapy
- Presence of intravascular catheters
- Repeated courses of broad-spectrum antibiotics
- Use of potent immunosuppressive regimens
- Colonization


Candidiasis Treatment

- Treatment for neutropenic patients
  - Echinocandin
  - Lipid Amphotericin B

- Duration of therapy
  - 2 weeks after documented clearance of *Candida* AND resolution of signs/symptoms (including neutropenia)


Mrs. Smith- Day 12

- Day 7 of cefepime
- VS: Tmax: 103; HR: 101; BP: 90/60; RR: 21; O₂: 99% on room air
- Initial blood cultures finalized as no growth
- ANC = 0
- Blood cultures are redrawn
Mrs. Smith- Day 12

What is/are the next step(s) in therapy management for her?

Aspergillus Species

• Ubiquitous mold
  – Soil, hay/grain, plants/trees

• Aspergillus
  – *A. fumigatus*
  – *A. flavus*
  – *A. niger*
  – *A. terreus*

Invasive Aspergillosis Clinical Presentation
Treatment of Aspergillosis

- Drug of choice
  - Voriconazole IV or PO
  - Be aware of CYP 450 drug interactions
- Alternative treatment
  - Lipid Amphotericin B
- Duration of therapy
  - 6–12 weeks
  - Duration of neutropenia

Summary

- Definitions of fever and neutropenia
- Pathogens implicated in neutropenic fever
  - Bacterial vs. fungal depends of duration of neutropenia
- High risk patients
  - Admit to hospital for IV antibiotics
- Empiric treatment considerations
  - Bactericidal
  - Anti-pseudomonal coverage

References

References