Infections in Immunocompromised Patients
TH 5001: Therapeutics III
Fall, 2003
Sara L. Lanfear, Pharm.D., BCPS

Required Reading


Content Questions:

1. Know how to calculate ANC
2. Define risk factors for infection in the febrile, neutropenic host
3. Be able to list common pathogens in the immunocompromised host
4. What tests should be performed to evaluate a febrile, neutropenic patient?
5. What factors put a person at low risk for severe infection?
6. Know which antibiotic regimens can be used as initial empiric therapy
7. What are the appropriate oral antibiotics that can be used in low risk patients?
8. When should vancomycin be added to the initial drug therapy for febrile neutropenia?
9. When should antifungal therapy be added to the febrile neutropenic patient?
10. Define the role of G-CSF and GM-CSF in the treatment of febrile neutropenia
11. List the most important monitoring parameters for a neutropenic patient
I. Introduction

A. Immunocompromised Host: Patient with intrinsic or acquired defects in host defenses
   - Predisposes patient to infections
   - Incidence is increasing as new aggressive therapies for diseases help patients live longer
   - Examples: HIV/AIDS, organ transplant and cancer (after undergoing myelosuppressive chemotherapy) patients

B. Infection remains the leading cause of autopsy-determined death in neutropenic cancer patients (6 to 30% of deaths)

II. Definitions

A. Absolute Neutrophil Count (ANC) = (% Segs or PMNs + % Bands) x WBC/100

B. Neutropenia
   - ANC < 1000 cells/mm³: reduction sufficient to predispose patients to infection
   - ANC < 500 cells/mm³: Critical value in making therapeutic decisions regarding management of infection.
   - ANC < 100 cells/mm³: Profound neutropenia--Patient is at even greater risk

C. Fever
   - Single oral temperature ≥ 38.3° C (101 F)
   - Temperature ≥ 38.0° C for ≥ 1 hour (100.4 F)

III. Risk Factors for Infection

A. Antineoplastics: see oncology lecture for list of chemotherapeutic agents

B. Rapidity of ANC decline

C. Duration of neutropenia
   - Depends on antineoplastic drug selected

D. Profound neutropenia

E. Altered skin defenses / foreign body
   - Central venous catheters
   - Urinary (Foley) catheter
   - Radiation induced skin damage / cellulitis
   - Surgery
   - Mechanical ventilation
   - Mucositis / stomatitis (translocation of bacteria across oral / GI mucosa)
F. Other Immune System Defects
   - Defects in T-lymphocyte and macrophage function (cell-mediated immunity)
     - Transplant patients receiving immunosuppressive drugs, such as cyclosporine, tacrolimus, mycophenolate, corticosteroids, or azathioprine
   - Defects in B-cell function (humoral immunity)
     - Usually caused by an underlying disease such as multiple myeloma, and chronic lymphocytic leukemia

IV. Infections
   A. Etiology
      - Primary site of infection often includes alimentary tract, and where there has been damage to the integument.
        - Febrile episodes can be attributed to microbiologically or clinically documented infection in ~30 to 40% of cases
      - Other causes of fever may be unrelated to infection
        - Reaction to blood products, chemotherapeutic agents, cell lysis and the underlying malignancy itself.
      - Most Common Organisms
        - Gram-positive cocci and bacilli: often the cause when there is an infected catheter
          - ~60 to 70% of microbiologically documented infections
          - Staphylococcus species (aureus, epidermidis, & others)
          - Streptococcus species (pneumonia, pyogenes, & viridans)
          - Enterococcus faecalis/faecium
          - Corynebacterium species
        - Gram-negative bacilli and cocci
          - E. coli
          - Klebsiella sp.
          - Pseudomonas aeruginosa
        - Fungal infections: usually superinfections
          - Candida sp or other fungi can cause primary infections
   B. Clinical Presentation
      - At least ½ of neutropenic patients who become febrile have an established or occult infection and 20% of patients with ANC < 100 have bacteremia
      - Signs and symptoms may be minimal or absent
      - Search should be undertaken for subtle signs and symptoms, including pain, at most commonly infected sites
• The periodontium, the pharynx, the lower esophagus, the lung, the perineum, the eye and the skin

C. Evaluation

• Thorough physical exam
• Cultures should be obtained immediately
  • At least 2 sets of cultures should be obtained; ≥ 1 set of blood samples obtained from a central venous access device (if one is in place) as well as from a peripheral vein
  • From any lesions suspected of being infected
  • Urine if there are any signs or symptoms of UTI or if abnormal urine analysis.
  • If diarrhea is present, stool cultures should be obtained
• Chest x-ray if any s/s of respiratory tract infections or if outpatient therapy is planned
• CBC
• SrCr, BUN and transaminases

V. Treatment

A. Empiric antibiotic therapy should be administered promptly. Also begin antibiotics if afebrile, but signs & symptoms of infection are present.

B. Initial Antibiotic Therapy

• Must consider site of potential infection, and the type, frequency of occurrence, and antibiotic susceptibility of bacterial isolates at the hospital.

• Remove any sources of infection if possible

```
Fever (temp > 38.3 + Neutropenia (<500 neutrophils/mm³)
```

- Low Risk
  - Oral
    - Ciprofloxacin + Amoxicillin-clavulanate (adults only)
  - IV
    - Monotherapy
      - Cefepime, Ceftazidime OR Carbapenem
    - Two Drugs
      - Aminoglycoside + Antipseudomonal pcn
      - Cefepime, Ceftazidime, OR Carbapenem ± aminoglycoside

- High Risk
  - IV
    - Vancomycin not needed
      - Vancomycin needed

Reassess after 3 – 5 days
• Factors that favor a low risk for severe infection
  • ANC > 100 and/or Absolute Monocyte Count > 100
  • Duration of neutropenia ≤ 7 days and resolution of neutropenia in ≤ 10 days
  • Normal CXR
  • No IV catheter-site infection
  • Normal hepatic and renal function
  • No appearance of illness (i.e., no abdominal pain, neurologic or mental changes, not hypotensive, etc)

• Indications for vancomycin use
  • Clinically suspected serious catheter related infection
  • Known colonization with resistant GP organism
  • Positive results of blood culture for GP bacteria before final identification or susceptibility testing
  • Hypotension or other evidence of cardiovascular impairment
  • Severe mucositis or pneumonitis in hospitals with high rates of MRSA and CoNS
  • Quinolone prophylaxis

• Monotherapy
  • Ceftazidime monotherapy does not cover gram +
  • Resistant organisms not covered

• Combination Therapy
  • Advantages

  • Disadvantages

Drug Doses (for patients with normal renal function)

<table>
<thead>
<tr>
<th>Drug Dose</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>1–2 g IV q 8–12 hours</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1 g IV q8 hours</td>
</tr>
<tr>
<td>Imipenem/cilastatin</td>
<td>500 mg IV q6 h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 gram IV q8 hours</td>
</tr>
<tr>
<td>Ticarcillin-clavulanic acid</td>
<td>3.1 grams IV q6h</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>3.375 gm IV q6h</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15 mg /kg IV q 12 hours</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>875 mg po BID</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500 mg po BID</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>5 mg/kg IV qd</td>
</tr>
</tbody>
</table>

• Drug Allergy
C. Management of the Antibiotic Regimen During the First Week of Therapy

- Patient afebrile within 3-5 days of Treatment
  - Therapy should continue for >7 days, until cultures are sterile and the patient has clinically recovered

**Afebrile within first 3-5 days of treatment**

- No etiology identified
  - Low Risk
    - Change to: Ciprofloxacin + Amoxicillin-clavulanate (adults) OR cefixime (child)
  - High Risk
    - Continue same antibiotics
- Etiology identified
  - Adjust to most appropriate treatment—broad spectrum coverage should be maintained

- Persistent fever throughout the first 3-5 days of treatment
  - Attempt to identify factors for non-responsiveness
    - Nonbacterial infection
    - Resistant bacterial infection
    - Emergence of a second infection
    - Inadequate serum and tissue levels of antibiotics
    - Infection at an avascular site (abscess or catheter)

**Persistent fever during first 3-5 days of tx: no etiology**

- Continue initial antibiotics
  - If no change in condition (consider stopping vanc)
- Change antibiotics
  - If progressive disease, if criteria for vanc are met
- Antifungal drug, with or without antibiotic change
  - If febrile through days 5-7 and resolution of neutropenia is not imminent
• Fungal therapy: usually to treat *Candida* or *Aspergillus*
  • Amphotericin B: 0.7 mg/kg (rarely up to 1 mg/kg)
  • Toxicities
    i. Infusion related
    ii. Nephrotoxicity—potentiated by nephrotoxic agents
    iii. Electrolyte imbalances
• Lipid formulations of amphotericin B
  • Similar efficacy, decreased side effects (infusion related and nephrotoxicity)
    i. Consider use in patients at risk for nephrotoxicity or if receiving other nephrotoxic agents
  • Much more expensive
  • Amphotericin B lipid complex (ABLC, Abelcet) – 5 mg/kg/day infused over a two hour period
  • Liposomal amphotericin B (Ambisome) – 3 to 5 mg/kg/day infused over 120 minutes
  • Amphotericin B colloidal dispersion (ABCD, Amphotec) – 3 to 4 mg/kg/day
• Fluconazole may be used if mold infections (*Aspergillus* sp) and drug-resistant *Candida* sp (*Candida krusei* and some strains of *Candida* glabrata) are uncommon

D. Duration of Antimicrobial Therapy
• Neutrophil count is the single most important determinant of successful discontinuation of antibiotics
• If afebrile by days 3 to 5
  • ANC ≥ 500 x 2 consecutive days: stop antibiotics 48 h after both afebrile and ANC ≥ 500
  • ANC < 500 by day 7:
    • If initially low risk and doing clinically well, stop antibiotics when afebrile for 5 to 7 days
    • If initially high risk (ANC <100, mucositis or unstable), continue antibiotics
• Persistent Fever
  • ANC ≥ 500: Stop 4 to 5 days after ANC > 500 and reassess
  • ANC < 500: Continue for 2 weeks. Then reassess. If no disease present and condition stable, discontinue.

E. Antivirals
• Antivirals (acyclovir, valacyclovir, and famciclovir) are indicated only if there is clinical or laboratory evidence of viral disease
  • skin or mucous membrane lesions due to herpes simplex or varicella-zoster
F. Use of Colony-Stimulating Factors

- G-CSF = Granulocyte colony-stimulating factor (filgrastim) or GM-CSF = Granulocyte–macrophage colony-stimulating factor (sargramostim)
- Can significantly shorten the duration of neutropenia, but have not consistently reduced other measures of febrile morbidity
- May be indicated when a worsening course is predicted and there is an expected long delay in recovery of the marrow
  - Pneumonia, hypotensive episodes, severe cellulitis or sinusitis, systemic fungal infections, and multi-organ dysfunction secondary to sepsis
- Not recommended for routine use

G. Non-Pharmacologic Therapy

- Neutropenic patients should be placed in reverse isolation
- Strict adherence to infection control guidelines
- Avoid fresh fruits and vegetables – frequently colonized with bacteria and fungi
- Personal hygiene

VI. Antibiotic Prophylaxis

A. Area of controversy—little consensus

- Data supports the efficacy of prophylaxis with TMP-SMX, quinolones, fluconazole, and itraconazole in reducing the number of infectious episodes during the neutropenic period
- Concern about emerging drug-resistant bacteria and fungi and no consistent reduction in mortality leads to recommendation that routine prophylaxis be avoided
- If given, antibiotics should be administered for a short time period and to as few patients as possible.
- Vancomycin prophylaxis should be discouraged

B. TMP-SMX is recommended for patients at risk for P. carinii pneumonia, regardless of neutropenia

VII. Monitoring

A. Patients need to be continually reassessed for evidence of infection and response to antimicrobial therapy.
B. Monitoring parameters will be based on type of infection patient has
C. Subjectively:
D. Objectively
  - CBC with differential
  - Vital signs
  - Physical exam
  - SrCr, BUN, electrolytes prn
  - Pertinent diagnostic tests
  - Drug specific monitoring