Neutropenic Sepsis: Critical Issues and Treatment Challenges

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  • Spectral Medical (EUPHRATES Sepsis Trial)
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Outline

- Definition, Epidemiology and Mortality of neutropenic sepsis
- Practice guidelines for antimicrobial therapy
- Biomarkers for febrile neutropenia
- Novel therapeutic approaches (IL-7, anti-PD1) for managing sepsis-immunosuppression
The Problem of Neutropenia

- Rising number of immunocompromised pts
- Changing epidemiology of infection
- Growing resistance to current antimicrobials
- Increasing risk of treatment-related infections
Neutropenic Sepsis

• Sepsis developing in patients receiving anticancer therapy with neutrophil count $<500/\text{mm}^3$ or $\leq 1000 \text{ mm}^3$ with expectation of further decline

AND

• Fever $\geq 38.3^\circ \text{C (101}^\circ \text{ F})$ or febrile state $(\geq 38.0^\circ \text{C (100.4}^\circ \text{ F})$ for $\geq 1$ hour

• Other S/Sx of significant sepsis
Factors Associated with Risk of Infection

- Duration and severity of neutropenia
- Type and intensity of chemotherapy regimen
- Altered phagocytic, cellular, or humoral immunity
- Breach of skin or mucosal barriers
- Catheters and other foreign bodies
- Underlying disease or therapy
- Corticosteroids
The total number of deaths has more than doubled from 2001-2010.

Mortality of Neutropenic Sepsis

- The total number of deaths has more than doubled from 2001-2010.
- Majority of deaths occur in the 65 to 79 age range.

Survival in neutropenic patients with severe sepsis/septic shock

Hospital survival 57% vs. 41%, p = .001

n=428

Survival of septic shock in cancer patients


n=3437
Mortality Trends in Critically Ill Cancer Patients

Advances in ICU supportive care
Neutropenic Sepsis: Clinical and Microbiologic Features

- Signs and symptoms of infection are often lacking.
- Fever alone may be the only indicator of infection.
  - Infection vs. noninfectious causes (ex: drugs, blood products, engraftment, cytokines)
- Common sites of infection: GI tract, lung, skin
  - ~10-25% will have a documented BSI; most occur in settings of prolonged or profound neutropenia (ANC<100).
- Rarely, fungal infections can account for first fevers.

Kalil AC, Opal SM. Curr Infect Dis Rep 2015;17:32
# Common Bacterial Pathogens in Neutropenic Patients

<table>
<thead>
<tr>
<th>Gram-positive Pathogens</th>
<th>Gram-negative Pathogens</th>
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<tbody>
<tr>
<td>Coagulase-negative staphylococci (most common blood isolates in most centers, low virulence)</td>
<td><em>Escherichia coli</em> (ESBL, carbapenemase-producing)</td>
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<tr>
<td>Enterococci (including VRE)</td>
<td><em>Klebsiella</em> species (ESBL, carbapenemase-producing)</td>
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<tr>
<td><strong>Staphylococcus aureus</strong> (including MRSA)</td>
<td><em>Pseudomonas aeruginosa</em> (MDR)</td>
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<tr>
<td><em>Streptococcus</em> species (including viridans group)</td>
<td><em>Enterobacter</em> species</td>
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<td><em>Citrobacter</em> species</td>
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<td><em>Xanthomonas maltophilia</em></td>
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<tr>
<td><em>Acinetobacter</em> species (MDR)</td>
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We have to be cognizant of resistant pathogens in the 21st century.
Fever & Neutropenia: Summary of Epidemiology

- Gram-positive pathogens now predominate in documented bloodstream infections.
  - CoNS accounts for majority but is associated with minimal virulence.

- Resistant organisms increasingly are causing infections:
  - PCN-R viridans streptococci
  - MRSA
  - VRE
  - MDR GNR

- No microbiologic diagnosis is established in majority of cases.
IDSA Guidelines: Management Principles

- Every patient with F&N should receive **prompt** empiric antibiotic therapy after presentation.

- IDSA Guidelines provide a framework for antimicrobial management.
  - Revision in late 2010.
  - Require constant re-evaluation as cancer therapies and related infections change over time.

- Changes in 2010 guidelines:
  - Emphasis on risk stratification (high vs. low-risk)
  - Empiric vs pre-emptive antifungal therapy
  - Updates on infection prevention

IDSA Guidelines: Initial Evaluation

- **HPI**
  - Nature, cycle/course of chemotherapy
  - Prophylactic agents, steroids, other immunosuppressive agents, growth factors
  - Previous infections (e.g., fungal infections, infections due to a resistant pathogen), previous procedures, allergies
  - Site-specific symptoms

- **Workup**
  - Blood cultures x2 (peripheral, catheter)
  - CBC, comprehensive metabolic panel
  - Chest radiograph (2010: if s/sx of lung infection)
  - Other cultures (urine, stool, skin lesions, drainage from any site) as warranted

Clinical Manifestations

- Cellulitis
- Ecthyma gangrenosum
- Marrow aspiration Site
- Perirectal abscess

Photos (clockwise) courtesy of Alison G. Freifeld, MD and Kent A. Sepkowitz, MD
Biomarkers to predict adverse events in febrile neutropenia

- Procalcitonin
- IL-6
- IL-8
- Mannose-binding lectin
- Presepsis (sCD14)

PCT in Diagnosis of Severe Infection in Patients with Febrile Neutropenia: Systematic Review and Meta-Analysis

- 27 studies, 1960 FN cases with PCT analysis
- 13 studies, 1710 FN cases with CRP; 5 studies, 314 FN cases with IL-6 analysis
- PCT had higher positive likelihood ratio (5.49) than CRP (1.82) and IL-6 (3.68).
- However, PCT also had high negative likelihood ratio (0.4) making decisions to stop antibiotics based on PCT alone difficult

Initial Antimicrobial Regimen for Neutropenic Fever

- Cover enteric and non-fermenting gram-negative bacilli
  - Meropenem 1 g IV q 8h or other carbapenem OR
  - Piperacillin-tazobactam 4.5 g IV q 6h OR
  - Cefepime 2 g IV q 8h (consider continuous infusion)
  - Add Metronidazole 500 mg IV q 8h if anaerobic infection associated with intra-abdominal infection, typhlitis, necrotizing soft tissue infections
- Add vancomycin 15 mg/kg IV q 12h until MRSA ruled out; if vanco intolerant, use linezolid 600 mg IV q 12h

Ciprofloxacin + Amoxicillin/clavulanate

- Oral
- IV

Low risk

Vancomycin not needed

High risk

Vancomycin needed

- Hemodynamic instability or other evidence of severe sepsis
- Pneumonia documented radiographically
- Positive blood culture for gram-positive bacteria, before final identification and susceptibility testing is available
- Clinically suspected serious catheter-related infection (eg, chills or rigors with infusion through catheter and cellulitis around the catheter entry/exit site)
- Skin or soft-tissue infection at any site
- Colonization with methicillin-resistant Staphylococcus aureus,
- Vancomycin-resistant enterococcus, or penicillin-resistant Streptococcus pneumoniae
- Severe mucositis, if fluoroquinolone prophylaxis has been given and ceftazidime is employed as empirical therapy

Selecting the Right Agent: Factors to Consider

- Antimicrobial spectrum
  - Gram-positive coverage (need for vancomycin?)
  - Anaerobic coverage seldom indicated

- Adverse events
  - Incidence of *C. difficile* infections
  - Drug allergies

- Antimicrobial resistance
  - Local susceptibility patterns
  - Incidence of MRSA, VRE, viridans streptococci
  - Incidence of MDR GNR
Selecting the Right Agent: Factors to Consider

- Aminoglycosides or FQs should NOT be used as monotherapy.
- Double β-lactam regimens (e.g., pip/tazo plus aztreonam) are discouraged due to $$ and toxicity without added benefit.
• Combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for pts with difficult to treat, MDR bacterial pathogens (e.g., Acinetobacter and Pseudomonas spp. (2B).
• Duration of therapy typically 7–10 days.
• Longer courses may be appropriate in pts who have a slow clinical response, undrainable foci of infection, bacteremia with S. aureus; some fungal and viral infections or immunologic deficiencies, including neutropenia (2C)

Crit Care Med 2013;31:946-55
Intensive Care Med 2013;39:165-228
De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study

44% De-escalation Rate
Antimicrobial de-escalation in septic cancer patients: is it safe to back down?

- n=105 adult cancer pts from ED to ICU, 01/2008-03/2013.
- 23% were neutropenic.
- 61 (58%) patients had de-escalation by ICU day 5.
- De-escalation group:
  - Shorter ICU LOS (8.1 vs. 11.2 days, P = 0.006)
  - Shorter Hospital LOS (17.1 vs. 23.4 days, P = 0.04)
  - ICU Mortality: 18% vs. 23% (0.62)
  - Hospital Mortality: 34% in both groups

Empiric Antifungal Therapy

- Low-risk patients: risk of invasive fungal infections is low, so routine use of empiric antifungal therapy is not warranted
- High-risk: empiric therapy recommended for pts with persistent or recurrent fever after 4-7 days of antibiotics, and whose overall duration of neutropenia is >7 days
  - Disseminated candidiasis is main concern
  - Monitor BD-glucan and serum galactomannan and check cultures for other opportunistic fungi
  - Rx: Voriconazole, Caspofungin, Amphotericin B lipid complex or liposomal amphotericin B

Antifungal Prophylaxis in Neutropenic Patients Receiving Chemotherapy and Stem Cell Transplant Recipients at Risk of Candidiasis

• For patients with chemotherapy-induced neutropenia:
  – Fluconazole 400 mg (6 mg/kg) daily (A-I)
  – Posaconazole 200 mg 3 times daily (A-I)
  – Caspofungin 50 mg daily (B-II)
  – Itraconazole 200 mg PO daily: effective alternative (A-I) but little advantage and less well tolerated.

• For SCT recipients with neutropenia:
  – Fluconazole 400 mg (6 mg/kg) daily
  – Posaconazole 200 mg 3 times daily
  – Micafungin 50 mg daily (A-I).

IDSA Guidelines: Colony-Stimulating Factors (CSFs)

- Prophylactic use should be considered for patients in whom the anticipated risk of fever and neutropenia is >20% (A-II).

- Not generally recommended for treatment of established fever & neutropenia (B-II).

Immunosuppression in Sepsis

Hotchkiss RS, Lancet Infect Dis 2013;13:260-68
Immunosuppression in Sepsis

- The longer the sepsis continues, the more likely the patient is to develop profound immunosuppression.

Hotchkiss RS, Lancet Infect Dis 2013;13:260-68
IL-7 Immunotherapy in Sepsis

Hotchkiss RS, Lancet Infect Dis 2013;13:260-68
Anti-PD-1 Immunotherapy in Sepsis

Hotchkiss RS, Lancet Infect Dis 2013;13:260-68
Mesenchymal Cells in Patients With Septic Shock and Severe Neutropenia: Promising?

- Significantly reduced mortality in septic mice receiving appropriate antimicrobial therapy.
- Reduces systemic inflammatory cytokine levels in mice, down-regulation of IL-10, IL-6.
- Bacterial clearance greater in MSC-treated mice.
- Safety shown by GVHD Rx MSCs in pts after HSCT.

Summary: Neutropenic Sepsis

- Cardinal signs of inflammation often lacking making early diagnosis a major challenge.
- Surviving Sepsis & IDSA guidelines provide a framework for diagnosis and antimicrobial Rx.
- Early effective antimicrobial Rx and hemodynamic resuscitation to reverse organ failure are keys to improving outcomes.
- Need for novel biomarkers & innovative treatment strategies (IL-7, anti-PD1, MSC).
Thank You

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