Febrile neutropenia, neutropenic fever, or fever and neutropenia?

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Disclosures

- Nothing to disclose
Objectives

Pharmacists:
- Define febrile neutropenia per Infectious Diseases Society of America (IDSA) and National Comprehensive Cancer Network (NCCN) guidelines
- Outline an empiric antimicrobial regimen for a patient with febrile neutropenia
- Recognize the differences between IDSA and NCCN febrile neutropenia guideline recommendations

Technicians:
- Define febrile neutropenia per Infectious Diseases Society of America (IDSA) and National Comprehensive Cancer Network (NCCN) guidelines
- Recognize the differences between IDSA and NCCN febrile neutropenia guideline recommendations
Pre-Test Questions

- True/False: Patient with 103 F fever and ANC of 1500 (not anticipated to decrease) meets the IDSA and NCCN criteria for febrile neutropenia.

- What is the best empiric treatment option for a patient presenting with febrile neutropenia of suspected urinary source?
  - Cefepime
  - Vancomycin
  - Cefazolin
  - No antibiotics needed

- True/False: All patients presenting with febrile neutropenia require G-CSF therapy.
I. What is the role of risk assessment and what distinguishes high-risk and low-risk patients with fever and neutropenia?

II. What cultures should be collected and what specific tests should be performed during the initial assessment?

III. In febrile patients with neutropenia, what empirical antibiotic therapy is appropriate and in what setting?

IV. When and how should antimicrobials be modified during the course of fever and neutropenia?

V. How long should empirical antibiotic therapy be given?

VI. When should antibiotic prophylaxis be given and with what agents?

VII. What is the role of empirical antifungal therapy and what antifungals should be used?

VIII. What is the role of hematopoietic growth factors (G-CSF or GM-CSF) in managing fever and neutropenia?
Definition (aka diagnosis criteria)

- **IDSA 2010 Update**
  - Fever (will develop during ≥1 chemo cycle): single oral temp  ≥38.3°C (101°F) or sustained ≥38°C (100.4°F) over 1 hour period
    - 10-50% of patients w/ solid tumors
    - >80% of patients w/ hematologic malignancies
  - Neutropenia: ANC <500 cells/mm³ or expected to decrease to <500 cells/mm³ during next 48 hours

- **NCCN 2018 Update**
  - Fever: Single oral temp  ≥38.3°C (101°F) or sustained ≥38°C (100.4°F) over 1 hour period
  - Neutropenia: <500 neutrophils/mcL or <1000 neutrophils/mcL and a predicted decline to ≤500/mcL over the next 48 hours

High vs Low Risk

NCCN

High Risk
- Anticipated prolonged and profound neutropenia (>7 days, ANC ≤100 cells/mm³)
- Significant medical co-morbid conditions (hypotension, pneumonia, new onset abdominal pain, neurologic changes)

Low Risk
- Anticipated brief neutropenic periods
- No or few comorbidities
- Candidate for oral empirical therapy

• Burden of febrile neutropenia with no or mild symptoms
• No hypotension (SBP >90 mmHg)

• No chronic obstructive pulmonary disease
• Solid tumor or hematologic malignancy with no previous fungal infection

• No dehydration requiring parenteral fluids
• Burden of febrile neutropenia with moderate symptoms
• Outpatient status

• Age <60 years

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Cultures

- Blood cultures x2 sets
- Urine culture
  - If s/sx UTI or urinary catheter
- Site specific
  - C. difficile
  - Skin
  - Vascular access
  - Viral cultures
  - CSF
Common Pathogens

1960's/1970's: Predominately Gram Negative Pathogens

1980's/1990's: Gram Positive Pathogens Predominate - increased use of indwelling catheters

Currently: Coagulase-negative staphylococci; Enterobacteriaceae and non-fermenting Gram-negative Rods

Rarely: Fungi or Molds
Empiric Therapy- Low Risk

IDSA
- Initial oral or IV empirical therapy in clinic or hospital setting
  - Ciprofloxacin **PLUS** amoxicillin/clavulanate
  - If receiving prophylaxis with fluoroquinolone, empiric therapy should not include a fluoroquinolone

NCCN
- Assessment to include social criteria (caregiver, telephone, access to emergency facilities, adequate home environment)
  - Ciprofloxacin **PLUS** amoxicillin/clavulanate
    - Clindamycin for PCN allergic patients in place of amoxicillin/clavulanate
  - Levofloxacin
  - Moxifloxacin
“Management of Patients With Febrile Neutropenia A Teachable Moment”

- 10-50% of patients with solid cancers
- 80% hematologic cancers
- 2012 estimated 91,650 adult hospitalizations for cancer-related neutropenia in US
  - Mean length of stay 9.6 days
  - Mean cost per hospitalization $24,770
  - 91,650 x $24,770 = $2,270,170,500.....more than $2 billion!

Woman in her 30s Stage 2A breast cancer
Came to ED with temp 38.6 C, Fatigue x2 hours, no other symptoms
Recently completed cycle 4 of doxorubicin and cyclophosphamide 7 days prior
Provider instructed her to check temp if having symptoms
ED Course:
Temp 38.4 C; BP 126/78 mmHg; HR 86 bpm; RR 14/min; Physical Exam Normal
ANC 420 cells/mcL; CMP normal; Chest X-ray Normal; Urinalysis Normal; Blood cultures pending

Teachable Moment

- Does she meet criteria for Low Risk or High Risk?
- Does she meet admission criteria?
- Admission course:
  - Started on Vancomycin and Piperacillin/Tazobactam
  - Day 2: ANC 1200 cells/mcL (no G-CSF given!); Blood cultures: no growth
  - Day 3: Planned discharge
    - SCr 1.9 mg/dL (baseline 0.7 mg/dL)
  - Day 6: Discharged, AKI associated with antibiotic use
- Could have received oral antibiotics, not been admitted, not developed AKI, and spent more time in the comfort of home….
  - We won’t discuss risk of MDRO acquisition!
Empiric Therapy - High Risk

- Anti-pseudomonal Beta-lactam
- Not part of standard recommendation:
  - Anti MRSA therapy
  - Antifungal therapy
Empiric Therapy Considerations

- At risk for infections with:
  - MRSA: Vancomycin, Daptomycin or Linezolid
  - VRE: Linezolid or Daptomycin
  - ESBLs: Carbapenem
  - KPCs: Polymyxin/colisitin; Tigecycline; Pipeline Antimicrobials
Modification?

- **De-escalation**
  - Guided by clinical and microbiologic data

- **Escalation**
  - Hemodynamically unstable or persistent fever?
    - Consider broadening coverage including addition of antifungal therapy
Case Review

CULTURE URINE

FINAL

>100,000 cfu/ml of Pseudomonas aeruginosa

<table>
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<th>Organism</th>
<th>Antibiotic</th>
<th>MIC</th>
<th>INTRP</th>
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<td>P.aeruginosa</td>
<td>Cefepime</td>
<td>2</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
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<tr>
<td></td>
<td>Gentamicin</td>
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<tr>
<td></td>
<td>Piperacillin/tazobactam</td>
<td>32</td>
<td>S</td>
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S = SUSCEPTIBLE I = INTERMEDIATE R = RESISTANT

DRUG COMMENTS:

D1: Requested
D2: Tested via KB method, therefore no MIC value reported.

For blood and CSF isolates, a beta-lactamase test is recommended for Enterococcus species.
Duration

- Duration is dependent on site of microbiologic infection
  - Pneumonia → treat for appropriate pneumonia duration
  - Pyelonephritis → treat for appropriate pyelonephritis duration
  - Osteomyelitis → treat for appropriate osteomyelitis duration
  - C. difficile → treat for appropriate C. difficile duration

- No microbiologic infection identified...
  - Treat until ANC ≥500 cells/mm³ and rising!
  - Make sure fever has resolved as well
Prevention

- **Antimicrobial Prophylaxis**
  - **Fluoroquinolones**
    - High risk with expected durations of prolonged and profound neutropenia

- **Antiviral Prophylaxis**
  - HSV seropositive undergoing HSCT or leukemia induction

- **Antifungal Prophylaxis**
  - **“Azole” antifungals**
    - *Candida* should be covered if risk of invasive infection is substantial (e.g. HSCT) or intensive remission-induction or salvage-induction for acute leukemia
  - **Aspergillus (Posaconazole)**
    - Intensive chemotherapy for AML/MDS with substantial risk
    - Prior to HSCT will depend on site specific protocols
Prevention - Vaccinations

- Influenza
- Pneumococcal
  - PCV13- newly diagnosed (naïve)
  - PPSV23 at least 8 weeks later
  - If PPSV23 previously received, PCV13 at least 1 year after last PPSV23
- Meningococcal
  - Persistent complement deficiencies, eculizumab or anatomic or functional asplenia
- HPV
  - Up to 26 years of age
- Travel vaccines
  - Per ID consult
- Zoster
  - Shingrex?
- Live vaccinations
  - NOT RECOMMENDED!!!!
- Remember household members!
Antifungal

**Azoles - spectrum varies**
- Fluconazole
- Isavuconazonium sulfate
- Itraconazole
- Posaconazole
- Voriconazole

Think drug-drug interactions and side effect profile!

**Amphotericin B - Candida, Aspergillus sp, Zygomycetes, Molds, Cryptococcus**
- Different dosing for different formulations!

Think side effect profile!

**Echinocandins - Candida, 2nd line combination therapy for Aspergillosis**
- Anidulafungin
- Caspofungin
- Micafungin

Think limited site of action, not for CNS, micafungin not for UTI!
G-CSF

- Multipotential hematopoietic stem cell (Hemocytoblast)
  - Common myeloid progenitor
    - Erythrocyte
    - Mast cell
    - Myeloblast
    - Megakaryocyte
      - Thrombocytes
    - Basophil
    - Neutrophil
    - Eosinophil
    - Monocyte
    - Macrophage

- Common lymphoid progenitor
  - Natural killer cell (Large granular lymphocyte)
  - Small lymphocyte
    - T lymphocyte
    - B lymphocyte
    - Plasma cell
G-CSF- To Use or Not to Use?

IDSA:
- Prophylactically:
  - Anticipated risk of fever and neutropenia is 20% and greater
- Treatment:
  - Not recommended for treatment of established fever and neutropenia

NCCN:
- Prophylactically:
  - Anticipated risk of fever and neutropenia is 10-20% and ≥1 risk factor present
- Treatment:
  - Follow chart

Assess patient risk factors:

- Patients receiving daily prophylactic filgrastim, filgrastim-sndz, or tbo-filgrastim:
  - Continue G-CSF
- Patients who have received long-lasting prophylactic pegfilgrastim:
  - No additional G-CSF
- Risk factors not present for an infection-associated complication:
  - No therapeutic MGF
- Risk factors present for an infection-associated complication:
  - Consider therapeutic MGF
EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH A HIGH RISK FOR FEBRILE NEUTROPENIA (>20%)³

- This list is not comprehensive; there are other agents/regimens that have a high risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for treatment by cancer site are considered when updating this list of examples.
- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia, MGF-2)
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive vs. heavily pretreated patients). (See MGF-1)

**Acute Lymphoblastic Leukemia (ALL)**
- Select ALL regimens as directed by treatment protocol (See NCCN Guidelines for ALL)

**Bladder Cancer**
- Dose-dense MVAC³ (methotrexate, vinblastine, doxorubicin, cisplatin)¹

**Breast Cancer**
- Dose-dense AC followed by T² (doxorubicin, cyclophosphamide, paclitaxel)²
- TAC (docetaxel, doxorubicin, cyclophosphamide)³
- TC³ (docetaxel, cyclophosphamide)⁴
- TCH³ (docetaxel, carboplatin, trastuzumab)⁵

**Hodgkin Lymphoma**
- Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)⁷

**Kidney Cancer**
- Doxorubicin/gemcitabine⁸

**Non-Hodgkin’s Lymphomas**
- Dose-adjusted EPOCH³ (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)⁹
- ICE (ifosfamide, carboplatin, etoposide)¹⁰,¹¹
- Dose-dense CHOP-14⁵ (cyclophosphamide, doxorubicin, vincristine, prednisone)¹²,¹³
- MINE (mesna, ifosfamide, mitoxantrone, etoposide)¹⁴
- DHAP (dexamethasone, cisplatin, cytarabine)¹⁵
-ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine)¹⁵
- HyperCVAD³ (cyclophosphamide, vincristine, doxorubicin, dexamethasone)¹⁷,¹⁸

**Melanoma**
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)¹⁹

**Multiple Myeloma**
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)¹⁰ ± bortezomib (VTD-PACE)²¹

**Ovarian Cancer**
- Topotecan²²
- Docetaxel²³

**Soft Tissue Sarcoma**
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)²⁴
- Doxorubicin²⁵
- Ifosfamide/doxorubicin²⁶

**Small Cell Lung Cancer**
- Topotecan²⁷

**Testicular Cancer**
- VeIP (vinblastine, ifosfamide, cisplatin)²⁸
- VIP (etoposide, ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)²⁹,³⁰
- TIP (paclitaxel, ifosfamide, cisplatin)³¹

See Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia, MGF-A (2 of 4)
Post-test Questions

- True/False: Patient with 103 F fever and ANC of 1500 (not anticipated to decrease) meets the IDSA and NCCN criteria for febrile neutropenia.

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