Febrile Neutropenia in Cancer

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www.fshp.org

Objectives

• Pharmacist
  – Define febrile neutropenia and the risk factors for developing an infection
  – Identify the different prophylactic treatment options for high risk patients
  – Recognize appropriate empiric therapy for initial treatment, based on guideline recommendations

• Technician
  – Identify patients who are at risk of developing febrile neutropenia
  – Indicate the time frame in which febrile neutropenia treatment should be initiated
  – Recognize healthcare worker actions that may reduce febrile neutropenia occurrence

Disclosure

• Nothing to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation

Guidelines

• NCCN: National Comprehensive Cancer Network
  – Cancer Related Infections: Prevention & Treatment
  – Myeloid Growth Factors

• ASCO: American Society of Clinical Oncology
  – Febrile Neutropenia: Prophylaxis & Outpatient Management
  – WBC Growth Factors

• IDSA: Infectious Diseases Society of America
  – Neutropenic Patients with Cancer: Antimicrobial Agent Use
### Abbreviations

- **ANC**: Absolute Neutrophil Count
- **CSF**: Colony Stimulating Factor
- **MDS**: Myelodysplastic Syndrome
- **AML**: Acute Myeloid Leukemia
- **ALL**: Acute Lymphocytic Leukemia
- **NHL**: Non-Hodgkin’s Lymphoma
- **HL**: Hodgkin’s Lymphoma
- **MM**: Multiple Myeloma
- **PS**: Performance Status
- **CVC**: Central Venous Catheter
- **CBC**: Complete Blood Cell Count
- **CMP**: Complete Metabolic Panel
- **PPI**: Proton Pump Inhibitor
- **HSCT**: Hematopoietic Stem Cell Transplant
- **GVHD**: Graft vs. Host Disease
- **HSV**: Herpes Simplex Virus
- **VZV**: Varicella Zoster Virus
- **CMV**: Cytomegalovirus
- **HBV**: Hepatitis B Virus
- **MRSA**: Methicillin Resistant S. Aureus
- **VRE**: Vancomycin Resistant Enterococcus
- **KPC**: K. pneumoniae carbapenemase
- **ESBL**: Extended Spectrum Beta Lactamase
- **PCP**: Pneumocystis jiroveci
- **MASCC**: Multinational Association for Supportive Care in Cancer
- **ECOG**: Eastern Cooperative Oncology Group

### Epidemiology

- **Incidence Varies**
  - Dependent on Risk Factors
  - Solid Tumors 10-50%
  - Hematologic Malignancy >80%
- **Clinically Documented Infection**
  - 20-30% of Febrile Neutropenia Cases

### Febrile Neutropenia

- **Fever**
  - Single temperature ≥38.3°C (101°F)
  - Sustained temperature ≥38.0°C (100.4°F) ≥1 hour
- **Neutropenia**
  - ANC <500/mcL
  - ANC <1000/mcL & expect a fall to <500/mcL within 48 hours

### Etiology

- **Bacteremia**
  - 10-20% of Patients with a Prolonged ANC <100/mcL
- **Common Infection Sites**
  - GI Tract
  - Sinus
  - Lung
  - Skin
- **Aspergillosis**
  - Life Threatening
  - Sinus/Lung
  - Primarily Neutropenia ≥ 2 Weeks
- **Mucositis**
  - Candida
  - Bacterial
### Pathophysiology

- **Hematopoietic Stem Cell**
- **Bone Marrow**
- **Multipotential Stem Cell**
- **Lymphoid Progenitor**
- **Eosinophil**
- **Neutrophil**
- **Monocyte/Macrophage**
- **Basophil**
- **Red Blood Cells**

### Presentation

- **Fever**
  - Only Sign

- **Lack Cardinal Signs**
  - Calor
  - Rubor
  - Tumor
  - Dolor

### Pathophysiology

- **Normal Epithelium**
- **Initiation**
- **Amplification**
- **Ulcration**
- **Healing**

### Risk Factors

- **Patient**
  - Age ≥ 65 years
  - Poor PS ≥ 2
  - Albumin < 35g/L
  - Comorbidities
    - Single 27%
    - Two 67%
    - Three (+) 125%
  - FN History
- **Cancer**
  - Diagnosis
    - AML
    - MDS
    - NHL
    - MM
    - Germ Cell
    - Soft Tissue
  - Incomplete Response
    - Persistent/Refractory
    - Progressive
    - Remission Unattained
  - Stage ≥ 2
- **Treatment**
  - Medication
    - >85% Dose Admin
    - Purine Analogs
    - Alemtuzumab
    - Steroids
    - High Dose Chemo
  - Mucositis grade ≥ 3
  - Neutropenia ≥ 7 days
  - Procedures
    - HSCT
    - Splenectomy
    - Radiation

---

Cancer Diagnosis & Risk

Chemotherapy Regimens
FN Risk ≥20%

Chemotherapy Nadir
- Nadir
  - Lowest Cell Counts Post Chemo
- Onset & Duration Varies
  - Typically 10-14 Days
  - Prolonged or Delayed

Prophylaxis

Chemotherapy Nadir

Nadir

- Lowest Cell Counts Post Chemo

Onset & Duration Varies

- Typically 10-14 Days
- Prolonged or Delayed

Prophylaxis
### Prophylaxis

<table>
<thead>
<tr>
<th>Risk</th>
<th>Criteria</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Solid Tumors</td>
<td>Bacterial: None, Fungal: None, Viral: None</td>
</tr>
<tr>
<td></td>
<td>Standard Chemo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutropenia &lt;7 Days</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Autologous HSCT</td>
<td>Bacterial: Yes, Fungal: Yes, Viral: Yes</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CLL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Purine Analogs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutropenia for 7 to 10 Days</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Allogeneic HSCT</td>
<td>Bacterial: Yes, Fungal: Yes, Viral: Yes</td>
</tr>
<tr>
<td></td>
<td>Acute Leukemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Induction/Consolidation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GVHD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>With Steroid &gt;20 mg/Day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alemtuzumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutropenia &gt;10 Days</td>
<td></td>
</tr>
</tbody>
</table>

NCCN Neutropenia: ANC<1000/mcL

### Antibacterial Prophylaxis Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Coverage</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>500 mg PO BID</td>
<td>Gram + (less) Gram - Atypical Pseudomonas</td>
<td>CYP1A2 Inhibitor, Renal Dosing</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg PO Daily</td>
<td>Gram + Gram - Atypical Pseudomonas</td>
<td>Preferred, Renal Dosing</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg PO Daily</td>
<td>Gram + Gram - Atypical Anaerobic (+/-) Pseudomonas</td>
<td>No Renal-Dosing</td>
</tr>
</tbody>
</table>

Class Effects: QT Prolongation, Tendonitis/Rupture, Impaired Absorption with Cation Binding

### Antifungal Prophylaxis

#### Intermediate & High Risk

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Prophylaxis</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>Fluconazole</td>
<td>-</td>
</tr>
<tr>
<td>MDS/AML (Neutropenic)</td>
<td>Fluconazole</td>
<td>While Neutropenic</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amphotericin B</td>
<td></td>
</tr>
<tr>
<td>Autologous HSCT (w/ Mucositis)</td>
<td>Fluconazole</td>
<td>While Neutropenic</td>
</tr>
<tr>
<td></td>
<td>Micafungin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
<td>Until GVHD Resolution</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amphotericin B</td>
<td></td>
</tr>
<tr>
<td>Auto &amp; Allogeneic HSCT (Neutropenic)</td>
<td>Fluconazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Micafungin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posaconazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amphotericin B</td>
<td></td>
</tr>
<tr>
<td>Allogeneic HSCT (w/ Mucositis)</td>
<td>Fluconazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Micafungin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posaconazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amphotericin B</td>
<td></td>
</tr>
<tr>
<td>Mucositis + MDS/AML (Neutropenic)</td>
<td>Fluconazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amphotericin B</td>
<td></td>
</tr>
</tbody>
</table>

NCCN Neutropenia: ANC<1000/mcL

### Antifungal Prophylaxis

#### Triazole Dose Coverage Considerations/Interactions

<table>
<thead>
<tr>
<th>Triazole</th>
<th>Dose</th>
<th>Coverage</th>
<th>Considerations/Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>400 mg PO/IV Daily</td>
<td>C. albicans, Other Dimorphic Fungi</td>
<td>CYP3A4 (Moderate)</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Load 300 mg PO/IV BID†Then 300 mg PO/IV Daily</td>
<td>Candida Aspergilosis, Dimorphic Fungi</td>
<td>Take With Food, Avoid PPIs</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>200 mg PO Q 12 Hrs 4 mg/kg IV Q 12 Hrs</td>
<td>Candida Aspergilosis, Dimorphic Fungi</td>
<td>Take With Food, Avoid PPIs</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>200 mg PO Q 12 Hrs</td>
<td>Candida Aspergilosis, Dimorphic Fungi</td>
<td>Tablet with Food†, Caution GFR, Cardio</td>
</tr>
</tbody>
</table>

Class Effects: Significant CYP3A4 Inhibition/Drug Interactions
† Posaconazole Tablet Dosing: ISMP Alert Regarding Tablet → Suspension Conversion
†† Itraconazole Suspension: Take on Empty Stomach

Antifungal Prophylaxis

**Echinocandin**
- **Micafungin**: 50-100 mg IV Daily for Candida, Aspergillus
- Hepatic Dosing Considerations

**Caspofungin**: 50 mg IV Daily for Candida, Aspergillus
- Hepatic Dosing Considerations

**Polyene**
- **Amphotericin B Lipid (ABLC)**: 2.5 mg/kg IV TIW for Candida, Aspergillus
- Dimorphic Fungi: Pre-Medicate: NSAID +/- Diphenhydramine OR APAP + Diphenhydramine/HCl
- Less Renal Toxicity than Non-Lipid/Liposomal

**Amphotericin B Liposomal (LAmB)**: 3 mg/kg IV TIW


Antiviral Prophylaxis

**Criteria**
- **Solid Tumor Standard Chemotherapy**: HSV: If Prior HSV Active Therapy + While Neutropenic

**Autologous HSCT**
- **Lymphoma**: HSV: Active Therapy + While Neutropenic
- **Multiple Myeloma CLL**: HSV: Active Therapy + While Neutropenic
- **Fumigaclor**: HSV: Active Therapy + While Neutropenic

**Acute Leukemia**
- **Induction**: HSV: Active Therapy + While Neutropenic
- **Consolidation**: HSV: Active Therapy + While Neutropenic

**Plasmapheresis Inhibitor**
- HSV: Active Therapy + While Neutropenic

**Cyclosporine, Tacrolimus & Dexamethasone Interaction**

**Polyene Dose Coverage Considerations**
- **Amphotericin B Lipid (ABLC)**: 2.5 mg/kg IV TIW
- **Amphotericin B Liposomal (LAmB)**: 3 mg/kg IV TIW

**Aspergillus**
- **Aspergillus fumigatus Isolates**: October 2011-2013

**Antiviral Prophylaxis Agents**

**Drug**
- **Acyclovir**: HSV: 400-800 mg PO BID, VZV: 800 mg PO BID, CMV: 800 mg PO QID
- **Valganciclovir**: CMV: 5-6 mg/kg/Day IV 5 Days/Week for 100 Days Post HSCT

**Coverage Considerations**
- **Nephrotic Syndrome**: Hydration
- **HHV-6**: Myelosuppression

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### Pneumonia Prophylaxis

<table>
<thead>
<tr>
<th>Infection</th>
<th>Criteria</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCP</td>
<td>All Steroids ≥20 mg/day 1 month Purine Analogs</td>
<td>Trimethoprim-Sulfamethoxazole</td>
</tr>
<tr>
<td></td>
<td>Alemtuzumab</td>
<td>Sulfur Allergy:</td>
</tr>
<tr>
<td></td>
<td>Temozolomide + Radiation</td>
<td>• Dapsone</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>Allogeneic HSCT Chronic GVHD - On Immunosuppressants</td>
<td>• Atovaquone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pentamidine</td>
</tr>
<tr>
<td>Chimeric HSCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PCP Prophylaxis Agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Considerations / Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim-Sulfamethoxazole</td>
<td>6/8 or 9/6 PO Daily</td>
<td>Renal Dosing CYP2A4, CYP2C9, Methotrexate &amp; Leucovorin</td>
</tr>
<tr>
<td></td>
<td>-DS PO TWI</td>
<td></td>
</tr>
<tr>
<td>Dapsone</td>
<td>-100 mg PO Daily</td>
<td>CYP2A4</td>
</tr>
<tr>
<td></td>
<td>-50 mg PO BID</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>-1500 mg PO Daily</td>
<td>Hepatic Dosing With Food</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>-300 mg via Nebulizer</td>
<td>Renal Dosing QT Prolongation Nebulized</td>
</tr>
<tr>
<td></td>
<td>Q 3-4 Weeks</td>
<td></td>
</tr>
</tbody>
</table>

**Influenza**

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Drug</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients ≥6 Months Not Receiving</td>
<td>Trivalent Inactivated Vaccine</td>
<td>Annually - Chemotherapy or Immunotherapy</td>
</tr>
<tr>
<td>- Anti-B Cell Ab</td>
<td></td>
<td>- Vaccinate ≥2 Weeks Prior to Therapy</td>
</tr>
<tr>
<td>- Induction/Consolidation</td>
<td></td>
<td>- HSCT</td>
</tr>
<tr>
<td>Household Members</td>
<td></td>
<td>- Vaccinate 4-6 Months Post HSCT</td>
</tr>
<tr>
<td>Healthcare Providers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure or Outbreak</td>
<td>Oseltamivir 75 mg PO Daily</td>
<td>Take with Food</td>
</tr>
<tr>
<td>Treatment</td>
<td>Zanamivir 2 PO Inhaleses Daily</td>
<td>May Cause Bronchospasm</td>
</tr>
</tbody>
</table>

**Influenza A or B Positive Result**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Considerations / Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir 75-100 mg PO BID</td>
<td>FDA Approved: 5 Days Immunocompromised 10 Days/Resolution</td>
</tr>
<tr>
<td>Zanamivir 2 PO Inhalations BID</td>
<td>Duration Based on Exposure</td>
</tr>
</tbody>
</table>

**Colony Stimulating Factors**

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Colony Stimulating Factors

- Primary Prophylaxis
  - Febrile Neutropenia Risk
  - Treatment Intent
    - Curative vs. Palliative

<table>
<thead>
<tr>
<th>Risk</th>
<th>Curative Intent</th>
<th>Prolong Survival</th>
<th>Manage Symptoms/Quality of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (&gt;20%)</td>
<td>CSF (1)</td>
<td>CSF (1)</td>
<td>CSF</td>
</tr>
<tr>
<td>Intermediate (10-20%)</td>
<td>Consider CSF</td>
<td>Consider CSF</td>
<td>Consider CSF</td>
</tr>
<tr>
<td>Low (&lt;10%)</td>
<td>No CSF</td>
<td>No CSF</td>
<td>No CSF</td>
</tr>
</tbody>
</table>

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Colony Stimulating Factors

- Secondary Prophylaxis
  - Prior FN
  - Prior Dose Limiting Neutropenia

- Treatment Use
  - Continue CSF if Receiving Prior to FN
  - Infection Complication Risk Factors

- Timing
  - Initiate One Day Post Chemo
  - Start up to 3-4 Days Post Chemo

NCCN. Myeloid Growth Factors. 1.2015.

Colony Stimulating Factors

- Filgrastim
  - Neupogen
  - Zarxio
  - Granix
  - 5 mcg/kg/day
  - Post Chemo: >24 Hour
  - Prior to Chemo: Not <24 Hour
  - Bone Pain
  - Respiratory Distress

- Pegfilgrastim
  - Neulasta
  - Single Dose
  - 6 mcg/kg
  - Post Chemo: >24 Hour
  - Prior to Chemo: Not <14 Days
  - Bleomycin Lung Toxicity

NCCN. Prevention and Treatment of Cancer Related Infections. 2.2015.

Filgrastim

http://www.neupogenhcp.com/chemotherapy-induced-neutropenia/
### Treatment

#### Outpatient vs. Inpatient

**Low Risk**
- Neutropenia <7 days
- ECOG PS 0-1
- MASCC Score ≥21
- No Renal Dysfunction
- No Hepatic Dysfunction
- No or Few Comorbidities
- Outpatient Status at Onset

**High Risk**
- ANC ≤100/mcL for ≥7 days
- Post Cytotoxic Therapy
- MASCC Score <21
- Significant Comorbidities
  - Hypotension
  - Pneumonia
  - Abdominal Pain
  - Mucositis (Grade 3-4)
  - Uncontrolled Cancer
  - Neurologic Changes

#### MASCC Score Index

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>FN Symptom Burden</td>
<td>5</td>
</tr>
<tr>
<td>- None</td>
<td>5</td>
</tr>
<tr>
<td>- Mild</td>
<td>5</td>
</tr>
<tr>
<td>- Moderate</td>
<td>3</td>
</tr>
<tr>
<td>- Severe</td>
<td>0</td>
</tr>
<tr>
<td>No Hypotension</td>
<td>5</td>
</tr>
<tr>
<td>- SBP &gt;90 mmHg</td>
<td>5</td>
</tr>
<tr>
<td>No Prior 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</td>
<td>2</td>
</tr>
<tr>
<td>No COPD</td>
<td>4</td>
</tr>
</tbody>
</table>

**Identify Low Complication Risk**
- Specific to cancer patients

**Low Risk**
- Score ≥21
- Outpatient Treatment

**High risk**
- Score <21
- Inpatient Treatment

#### Outpatient Factors

- Caregiver, Phone & Transportation Available
- Medical Access 24/7
- Within 1 Hour Distance
- GI Function
  - Able to Tolerate & Absorb PO
  - No Nausea or Vomiting
- Upward Trending Cell Count
- No Fluoroquinolone Prophylaxis
- No Critical Labs

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Empiric Treatment

Outpatient

- Initial Dose In Hospital
  - Initiate Within 1 Hour
  - Observe 2-24 Hours
    - Persistent Fever → Admit → Inpatient
  - Stable → Discharge → Outpatient

Regimen | Dose | Considerations
--- | --- | ---
Ciprofloxacin + Amoxicillin/Clavulanate | Both: 500 mg PO Q 8 Hr | Category 1
MoXifloxacin | 400 mg PO Daily | Category 1
Ciprofloxacin + Clindamycin | Cipro: 500 mg PO Q 12 Hr | Pencillin Allergy Alternative

Inpatient Empiric Treatment

- Monotherapy
  - Pseudomonas Active Beta Lactam

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>4.5 gm IV Q 6 Hr</td>
<td>Intra-abdominal</td>
</tr>
<tr>
<td>Mersopenem</td>
<td>1-2 gm IV Q 8 Hr</td>
<td>CNS, Intra-abdominal, Lung</td>
</tr>
<tr>
<td>Imipenem-Cilastatin</td>
<td>500 mg IV Q 6 Hr</td>
<td>Intra-abdominal, Lung</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2 gm IV Q 8 Hr</td>
<td>CNS, Not Anaerobe/Enterococcus</td>
</tr>
</tbody>
</table>

Outpatient Monitoring

- Daily
  - In Person First 72 Hours
  - Phone Thereafter

- Return for
  - Positive Cultures
  - New Signs or Symptoms
  - PO Regimen Intolerance
  - Persistent or Recurrent Fever at 3-5 Days

Empiric Treatment Inpatient

- Combination Therapy
  - Complications or Resistance
    - Add Aminoglycoside
    - Clinically Unstable
    - Add Aminoglycoside + Vancomycin +/- Anti fungal
    - Vancomycin Not Used Empirically
    - Qualifying Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin, Gentamicin or Tobramycin</td>
<td>Single Loading Dose</td>
<td>Gram +</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15 mg/kg IV Q 12 Hr</td>
<td>Gram +, MRSA</td>
</tr>
</tbody>
</table>
Empiric Vancomycin Indications

- Colonization: MRSA or PCN resistant S. pneumoniae
- Positive Blood Culture with Gram Positive Bacteria
- Hemodynamic Instability or Severe Sepsis
- Central Catheter Related Infection
- Skin or Soft Tissue Infection

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Suspected Resistance

- Resistant Microbe
  - Prior Infection or Colonization
  - Suspected + Positive Blood Culture
  - Highly Endemic to Hospital

<table>
<thead>
<tr>
<th>Microbe</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>Vancomycin, Daptomycin or Linezolid</td>
</tr>
<tr>
<td>VRE</td>
<td>Linezolid, Daptomycin or Quinupristin/Dalfopristin</td>
</tr>
<tr>
<td>ESBL</td>
<td>Carbapenem</td>
</tr>
<tr>
<td>KPC</td>
<td>Polymyxin-colistin or Tigecycline</td>
</tr>
</tbody>
</table>


Inpatient Monitoring

- Daily
  - Site Specific H&P
  - Lab & Culture Review
  - Repeat Cultures
    - Document First Day of Clearance
- Twice Weekly
  - Drug Toxicity
  - Renal & Hepatic Function
- Day 3-5
  - Response
    - Fever Trends
    - Symptom Improvement

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Treatment Modification

- Hemodynamic Instability
- Persistent
  - Fever
  - Positive Blood Culture
- Coverage
  - Gram Positive
  - Gram Negative
  - Fungal
  - Candida
  - Resistant Microbes

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### Site Specific Considerations

<table>
<thead>
<tr>
<th>Site</th>
<th>Additional Agents</th>
</tr>
</thead>
</table>
| Mucosa/Esophagus     | Anaerobic Coverage
|                      | Thrush: Fluconazole (Cat 1)
|                      | Vesicular: Anti-HSV (Cat 1)
|                      | Consider Anti-CMV & Systemic Antifungal |
| Sinus/Nasal          | Broad Spectrum Aerobic & Anaerobic
|                      | Aspergillosis: Voriconazole (Cat 1) or Lipid Amphotericin B |
| Lung Infiltrates     | Atypical Coverage
|                      | PGP: Trimethoprim/Sulfamethoxazole
|                      | Suspected MRSA: Vancomycin or Linezolid
|                      | Intermediate /High Risk: Anti-Mold
|                      | Influenza Outbreak: Neuraminidase Inhibitor |

**Antifungal Addition**

**• Empiric Anti-Mold Therapy**
- Persistent or Recurrent Fever
- Post 4-7 Days Empiric Antibiotics

<table>
<thead>
<tr>
<th>Anti-Mold Agent</th>
<th>Dose</th>
<th>Coverage</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin</td>
<td>70 mg IV x1 Dose Then 50 mg IV Daily</td>
<td>Candida</td>
<td>Hepatic Dosing</td>
</tr>
<tr>
<td>Voriconazole(2)</td>
<td>6mg/kg IV Q 12 Hr x4 3-4mg/kg IV Q 12 Hr 200mg PO Q 12 Hr</td>
<td>Candida Aspergillus</td>
<td>On Empty Stomach CYP3A4, CYP2C9 &amp; CYP2C19 Interactions</td>
</tr>
<tr>
<td>Amphotericin B Lipid(2)</td>
<td>5mg/kg/day IV</td>
<td>Candida Aspergillus Dimorphic</td>
<td>Pre-medicate: NSAID +/- Diphenhydramine OR APAP + Diphenhydramine/HC Less Renal Toxicity than Non-Lipid/Liposomal</td>
</tr>
<tr>
<td>Amphotericin B Liposomal(2)</td>
<td>≥3mg/kg/day IV</td>
<td>Candida Aspergillus Dimorphic</td>
<td></td>
</tr>
</tbody>
</table>

**Site Specific Considerations**

<table>
<thead>
<tr>
<th>Site</th>
<th>Additional Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>Anaerobic Coverage</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>C. difficile: Metronidazole, Vancomycin PO or Fidaxomicin</td>
</tr>
</tbody>
</table>
| Cellulitis/SSTI     | Gram Positive Coverage
|                      | Peritonitis: Vancomycin
|                      | Disseminated Vancomycin
|                      | Disseminated + High Risk: Anti-mold
|                      | Vesicular: Acyclovir, Famciclovir or Valacyclovir
|                      | Perineal: Gram Negative + Anaerobic Coverage |
| CNS                 | Cefepime + Vancomycin + Ampicillin or Cefazidime + Vancomycin + Ampicillin or Meropenem + Vancomycin
|                      | Encephalitis: Acyclovir |
| CVC                 | Pocket/Tunnel Infection: Vancomycin +/- Catheter Removal |

**Treatment Modification**

- **Discontinue Vancomycin**
  - Within 2-3 Days of Initiation
  - If No Gram Positive Evidence
- **Low Risk Stable Patient**
  - Simplify Regimen
  - Discharge
- **Coverage Specific to:**
  - Site
  - Isolated Microbe
General Treatment Timing

- ASCO: Initiate Therapy ≤1 Hour from Triage

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained Fever</td>
<td>Rising Neutrophil Count ≥500/mcL + Afebrile &gt;24 Hours</td>
</tr>
<tr>
<td>Documented Infection</td>
<td>Appropriate to Site and Microbe + ANC ≥500/mcL</td>
</tr>
<tr>
<td>Infection Resolved + Neutropenic</td>
<td>Consider Change to Prophylaxis Regimen</td>
</tr>
</tbody>
</table>

Flowers CR, et al. ASCO. 2012
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Healthcare Professional Precautions

- Hand Hygiene
  - Entry & Exit
  - Soiled → Soap & Water
- Report Illness & Exposure
  - Active Cold Sore
- Vaccinations
  - Annual Influenza
  - MMR & Varicella
- Cough Etiquette
- Standard Barrier Precaution

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Environmental Precautions

- Private Room
- HEPA Filtration
- Air Exchange >12/Hour
- Infection Specific Isolation
- No Sick Visitors
- No Plants or Flowers
- No Animals
- Avoid Construction & Demolition

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NO SICK VISITORS OR PERSONNEL
NO PLANTS OR FLOWERS

Flowers CR, et al. ASCO. 2012
NCCN. Prevention and Treatment of Cancer Related Infections. 2.2015.

Treatment Duration

<table>
<thead>
<tr>
<th>Duration</th>
<th>Infection Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-10 Days</td>
<td>Influenza</td>
</tr>
<tr>
<td>7-10 Days</td>
<td>HSV/VZV (localized/uncomplicated)</td>
</tr>
<tr>
<td>7-14 Days</td>
<td>SSTI</td>
</tr>
<tr>
<td>10-14 Days</td>
<td>Bacteremia (gram pos/ uncomplicated)</td>
</tr>
<tr>
<td>≥2 Weeks</td>
<td>S. Aueus Bacteremia</td>
</tr>
<tr>
<td></td>
<td>Yeast Bacteremia</td>
</tr>
<tr>
<td></td>
<td>Candida</td>
</tr>
<tr>
<td>≥12 Weeks</td>
<td>Aspergillus or Mold</td>
</tr>
</tbody>
</table>

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Summary

• Febrile Neutropenia
  – Fever: Single Temp 101°F or Sustained 100.4°F for ≥1 Hour +
  – ANC < 500/mcL or < 1000/mcL ≤ 500/mcL within 48 Hours

• Prophylaxis
  – ANC ≤ 1000/mcL for ≥7 Days
    • Fluoroquinolone
    • Triazole
    • Nucleoside Analogue
  – FN Risk > 20% → CSF

• Empiric Treatment
  – Within 1 Hour
    • MASCC ≥ 21 → Outpatient → Cipro + Amox/Clav or Moxifloxacin
    • MASCC < 21 → Inpatient → PSA Active BL Monotherapy

• Healthcare Provider Prevention
  – Hand Hygiene + Vaccination → Reduced FN Incidence

References


• CDC. Cover Your Cough. CDC 2016; http://www.cdc.gov/flu/protect/covercough.htm


