Prevention is the Best Medicine: Antimicrobial Prophylaxis in the Hematology & Oncology Population

Hilary Teaford, Pharm.D.
Pharmacy Grand Rounds
9/25/2018
Objectives

• Describe considerations for the appropriate selection of antimicrobial prophylaxis in cancer patients

• Review appropriate dosing, side effects, and duration of antimicrobial agents for antifungal, antibacterial, and antiviral prophylaxis

• Identify some select agents in hematology which require unique antimicrobial prophylaxis considerations
Infection Risk in Cancer Patients

- Impaired Immunity
- Neutropenia
- Chemotherapy
- Gut Translocation
- Steroids
- Central lines

INFECTION
Type of Infection Risk by Immune Deficit

Innate Immunity

- Neutrophils
  - Bacterial, fungal and some viral\(^1\)
- Natural Killer Cells
  - Viral

Acquired Immunity

- Antibody-Mediated (B cell)
  - Viral reactivation
- Cell-Mediated (T cell)
  - CD\(4^+\) helper T cells
  - Pneumocystis jirovecii (PJP)

Complement

- Encapsulated bacteria

Hematopoiesis

**Lymphoid Line = ACQUIRED IMMUNITY**

- **ALL**
  - Lymphoid Progenitor
  - B
  - T
- **CLL**
  - B
  - Naive
- **Lymphoma**
  - T
- **MM**
  - Plasma Cells

**Myeloid Line = INNATE IMMUNITY**

- **AML, MDS, AA**
  - Myeloid Progenitor
  - Neutrophils
  - Eosinophils, Basophils, Monocytes

ALL = Acute Lymphocytic Leukemia, AML = Acute Myeloid Leukemia, CLL = Chronic Lymphocytic Leukemia, MM = Multiple Myeloma, MDS = myelodysplastic syndrome, AA = Aplastic Anemia
Common Bacterial Pathogens

- Escherichia coli
- Enterococcus species
- Staphylococcus coag. Neg
- Staphylococcus aureus
- Pseudomonas aeruginosa
- Klebsiella/Raoultella
- Viridans Group Streptococcus
- Enterbacter Cloacae Complex

Most Common Isolates in Hem./Onc. Patients at Mayo Clinic Hospital—Rochester 2016-2017
Common Bacterial Pathogens

Escherichia coli
Enterococcus species
Staphylococcus coag. Neg
Staphylococcus aureus
Pseudomonas aeruginosa
Klebsiella/Raoultella
Viridans Group Streptococcus
Enterbacter Cloacae Complex

Infection Sources:
Chemotherapy-Induced Mucosal Damage
Catheter Sites

Most Common Isolates in Hem./Onc. Patients at Mayo Clinic Hospital—Rochester 2016-2017
Optimal Antimicrobial Prophylaxis: Meta-Analysis

Relative All-Cause Mortality Reduction vs. Placebo in Afebrile Neutropenic Patients

- Any Quinolone
- SMZ-TMP 800-160 mg PO BID


SMZ-TMP: sulfamethoxazole-trimethoprim
## Agents Used in Antibacterial Prophylaxis

<table>
<thead>
<tr>
<th>Line</th>
<th>Drug</th>
<th>Considerations in Hem./Onc. Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>Levofloxacin(^1)</td>
<td>• Reported QTc prolongation (possibly less with Ciprofloxacin(^2))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Levofloxacin= more strep. viridans coverage</td>
</tr>
<tr>
<td>Next preferred</td>
<td>Ciprofloxacin</td>
<td></td>
</tr>
</tbody>
</table>

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2. Briasoulis. Cardiology. 2011. 120 (2) 103–110  
Defining Neutropenia

- **Neutropenia Defined by NCCN:**
  - Absolute Neutrophil Count (ANC) less than 500 neutrophils/mcL
  - OR
  - ANC less than 1000 neutrophils/mcL with expected drop to <500 neutrophils/mcL within 48 hours

- **Profound Neutropenia:** <100 neutrophils/mcL

- **Prolonged Neutropenia:** >7 days
## Risk of Bacterial Infections in Cancer Patients

NCCN Guidelines: Consider **fluoroquinolone** prophylaxis throughout course of neutropenia if expected **ANC <1000** for **>7 days**

<table>
<thead>
<tr>
<th>Solid Tumors</th>
<th>Low: less myelosuppressive chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Myeloma</td>
<td>Intermediate: regimen specific</td>
</tr>
<tr>
<td>CLL Lymphoma</td>
<td>VDT-PACE</td>
</tr>
<tr>
<td></td>
<td>CODOX-M/IVAC</td>
</tr>
<tr>
<td></td>
<td>R-CHOP14</td>
</tr>
<tr>
<td>Acute Leukemia</td>
<td>High: myelosuppression needed for treatment efficacy</td>
</tr>
<tr>
<td>• AML</td>
<td></td>
</tr>
<tr>
<td>• ALL</td>
<td></td>
</tr>
</tbody>
</table>
Emerging Controversy: Multiple Myeloma Fluoroquinolone Prophylaxis

977 Newly Diagnosed Multiple Myeloma Patients >21 years old

Placebo x 12 weeks

Levofloxacin 500 mg PO qd x 12 weeks

↓ composite of fever/all-cause mortality with levofloxacin after 12 weeks
↓ gram negative infections with levofloxacin
Same amount of C.diff, MRSA or ESBLs

Weaknesses: composite outcome, neutropenia grouping
# Primary Fungal Organisms of Concern

<table>
<thead>
<tr>
<th>Organism</th>
<th>Mortality in Invasive Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida (most common)</td>
<td>30%(^1)</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>40-90%(^2)</td>
</tr>
<tr>
<td>Mucor</td>
<td>54%(^3)</td>
</tr>
</tbody>
</table>

## Agents Used in Fungal Prophylaxis

### Azole class effects: LFT elevations, most prolong QTc, CYP inhibition

<table>
<thead>
<tr>
<th>Drug</th>
<th>Safety and Convenience Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spectrum: most candida</strong></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Among azoles less potent CYP 3A4 inhibition</td>
</tr>
</tbody>
</table>
# Recommendations for Select Patient Groups

<table>
<thead>
<tr>
<th>Population</th>
<th>Antifungal Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Risk</strong></td>
<td>None in most cases</td>
</tr>
<tr>
<td>Solid Tumors</td>
<td></td>
</tr>
<tr>
<td><strong>Medium Risk</strong></td>
<td>Preferred: fluconazole or an echinocandin during prolonged neutropenia</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td></td>
</tr>
<tr>
<td>CLL</td>
<td></td>
</tr>
<tr>
<td><strong>High-Risk</strong></td>
<td>Preferred: posaconazole during prolonged neutropenia</td>
</tr>
<tr>
<td>AML</td>
<td></td>
</tr>
<tr>
<td><strong>Preferred:</strong> fluconazole or an echinocandin during prolonged neutropenia</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>Alternate: amphotericin B during prolonged neutropenia</td>
</tr>
</tbody>
</table>

Prevention and Treatment of Cancer-Related Infections. NCCN. Version 1.2018
Isavuconazole as Prophylaxis for Invasive Fungal Infections (IFI)

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Design and Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornely 2015</td>
<td>20</td>
<td>Phase 2 Dose Escalation study in AML primary ppx</td>
<td>No major ADEs, 10% patients had breakthrough IFI</td>
</tr>
<tr>
<td>Rausch 2018</td>
<td>100</td>
<td>Retrospective study in primary ppx leukemia patients</td>
<td>18% of primary ppx pts had breakthrough IFI</td>
</tr>
<tr>
<td>Fung 2018</td>
<td>5</td>
<td>Case Series</td>
<td>5 cases of breakthrough IFI, 3/5 primary ppx</td>
</tr>
</tbody>
</table>

Ppx: Prophylaxis
ISA= Isavuconazole
ADE= Adverse Drug Event

Fung et al. Clin Infect Dis. 2018
# Viral Pathogens of Concern

<table>
<thead>
<tr>
<th>Virus</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV- Herpes Simplex Virus</td>
<td>Skin lesions, meningitis, blindness, encephalitis</td>
</tr>
<tr>
<td>VZV- Varicella Zoster Virus</td>
<td>Rash, neuritis, aseptic meningitis, neuropathy, encephalitis, pneumonitis, hepatitis, pancreatitis</td>
</tr>
<tr>
<td>HBV- Hepatitis B Virus</td>
<td>Acute hepatitis, chronic liver disease, cirrhosis, and hepatocellular carcinoma</td>
</tr>
<tr>
<td>CMV- Cytomegalovirus</td>
<td>Colitis, hepatitis, encephalitis, myocarditis, retinitis, Guillen-Barre syndrome</td>
</tr>
</tbody>
</table>
### Antiviral Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Prophylactic Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HSV/VZV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acyclovir</td>
<td>400-800 mg PO BID OR 5 mg/kg IV qd</td>
<td>Need hydration to avoid crystal nephropathy, renally dosed</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>500 mg PO BID or TID</td>
<td>Renally dosed</td>
</tr>
</tbody>
</table>

- **CMV (also covers HSV/VZV)**
  - Ganciclovir 5 mg/kg IV q12h x 7-14 days
  - Marrow suppression, renally dosed
  - Valganciclovir 900 mg PO qd

- **HBV**
  - **Entecavir:** *Preferred*
    - 0.5 mg PO qd
    - Renally dosed
    - Black box warning: lactic acidosis, hepatomegaly with steatosis
  - **Tenofovir:** *Preferred*
    - TDF: 300 mg PO qd
    - TAF: 25 mg PO qd
  - Lamivudine 100 mg PO qd

- **Bacterial**
- **Fungal**
- **Viral**
- **Pneumocystis**
- **Unique Agents**
Type of Infection Risk by Immune Deficit

**Innate Immunity**
- **Neutrophils**
  - Bacterial, fungal and some viral\(^1\)
- **Natural Killer Cells**
  - Viral

**Acquired Immunity**
- **Antibody-Mediated (B cell)**
  - Viral reactivation
- **Cell-Mediated (T cell)**
  - CD4\(^+\) helper T cells
  - Pneumocystis jirovecii (PJP)

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\(^1\) Galani. *J. Leukoc. Biol.* 2015. 98 (4) 557–564.
## Populations Needing Antiviral Prophylaxis

<table>
<thead>
<tr>
<th>Population</th>
<th>Type of Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged Neutropenia (ALL/AML most likely)</td>
<td>HSV during neutropenia or longer</td>
</tr>
</tbody>
</table>
Summary of Antiviral, Antifungal and Antibacterial Prophylaxis

• **AML**
  - During neutropenia: levofloxacin, posaconazole & acyclovir*

• **ALL**
  - During neutropenia: levofloxacin, fluconazole(or an echinocandin), acyclovir*

• **CML/MM/Lymphoma:**
  - Same as ALL during prolonged neutropenia
  - Refer to concomitant medications for antivirals to continue throughout therapy

• **Any patient**
  - Acyclovir throughout therapy if past episode of HSV

*Acyclovir may be continued throughout therapy
Case for Assessment Question 1

A patient with AML, recently discharged following count recovery is admitted due to pneumonia. She is started on cefepime. She is on levofloxacin, posaconazole and acyclovir prior to admission. Her ANC>2000 neutrophils/mcL.
What should you do with the levofloxacin & posaconazole?

A) Keep both

B) Keep the levofloxacin, discontinue the posaconazole

C) Discontinue both

D) Discontinue the posaconazole, keep the levofloxacin
What should you do with the levofloxacin & posaconazole?

A) Keep both
B) Keep the levofloxacin, discontinue the posaconazole
C) Discontinue both
D) Discontinue the posaconazole, keep the levofloxacin
**Pneumocystis jirovecii (PJP)**

- Caused by fungus *Pneumocystis jirovecii*
- Overall mortality in non-HIV patients = 30.6%\(^1\)
- Prophylaxis leads to 85% reduction in PJP\(^2\)

<table>
<thead>
<tr>
<th>Line of Therapy(^3)</th>
<th>Drug</th>
<th>Dose</th>
<th>Reasons to not use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>SMZ-TMP</td>
<td>Bactrim SS(^©): 400-80 mg PO qd</td>
<td>• Methotrexate use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bactrim DS(^©): 800-160 mg PO 3x weekly</td>
<td>• May cause myelosuppression</td>
</tr>
<tr>
<td>Alternate</td>
<td>Pentamidine</td>
<td>300 mg inhaled through nebulizer every 4 weeks following albuterol neb</td>
<td>Breakthrough PJP in upper lobe</td>
</tr>
<tr>
<td></td>
<td>Dapsone</td>
<td>100 mg PO daily</td>
<td>G6PD deficiency</td>
</tr>
<tr>
<td></td>
<td>Atovaquone</td>
<td>1500 mg daily of oral-suspension with high-fat meal</td>
<td>• Bad taste</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Must take with food</td>
</tr>
</tbody>
</table>

\(^1\) Liu Y et al. Oncotarget. 2017;8(35)
\(^3\) Prevention and Treatment of Cancer-Related Infections. NCCN. Version 1.2018

*SMZ-TMP*: sulfamethoxazole-trimethoprim
Type of Infection Risk by Immune Deficit

Innate Immunity

- Neutrophils
  - Bacterial, fungal and some viral\(^1\)
- Natural Killer Cells
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Acquired Immunity

- Antibody-Mediated (B cell)
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## PJP Prophylaxis: Patient Populations

<table>
<thead>
<tr>
<th>PJP ppx is recommended per NCCN</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose steroids</td>
<td>ALL, lymphoma, multiple myeloma, CNS disease</td>
</tr>
<tr>
<td>Temozolomide + radiation</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>CLL, lymphoma</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>CLL</td>
</tr>
<tr>
<td>T-Cell depleting agents: purine analogs (fludarabine, cladribine)</td>
<td>CLL (FCR), AML (CLAG-M, FLAG-M)</td>
</tr>
</tbody>
</table>

### Other PJP risk factors

<table>
<thead>
<tr>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine¹</td>
</tr>
<tr>
<td>Bendamustine²</td>
</tr>
<tr>
<td>Rituximab³</td>
</tr>
</tbody>
</table>

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### Risk of PJP in Intermittent Steroid Use

**Intermittent Courses of Corticosteroids Also Present a Risk for *Pneumocystis* Pneumonia in Non-HIV Patients: Calero-Bernal et. al. 2016**

<table>
<thead>
<tr>
<th>Design</th>
<th>Descriptive review of 128 cases of PJP, most without PJP ppx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results</strong></td>
<td>• 50% of patients had hematological disease</td>
</tr>
<tr>
<td></td>
<td>• ~20% patients used steroids intermittently with chemotherapy (equiv. 70 mg of prednisone per day)</td>
</tr>
<tr>
<td></td>
<td>• Rituximab, methotrexate and everolimus most common other immunosuppressive agents in cases</td>
</tr>
</tbody>
</table>

**Takeaway:** intermittent steroids with chemotherapy may also be risk factor for PJP
### Duration of Therapy for PJP Prophylaxis

<table>
<thead>
<tr>
<th>Group</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
<td>For 2 months and until CD4(^+) count is greater than 200 cells/mcL</td>
</tr>
<tr>
<td>Other T-cell depleting therapies</td>
<td>Until CD4(^+) count is greater than 200 cells/mcL</td>
</tr>
<tr>
<td>(purine analogs)</td>
<td></td>
</tr>
</tbody>
</table>

Case for Assessment Question #2

A Multiple Myeloma patient being treated with weekly CyBorD (Cyclophosphamide-Bortezomib-Dexamethasone) is admitted for pneumonia. Dexamethasone is given 40 mg (267 mg prednisone equivalent) weekly. He has SMZ-TMP and acyclovir as home meds. His ANC is >2000 neutrophils/mcL
What should you do with his SMZ-TMP and acyclovir?

A. Discontinue both agents
B. Keep SMZ-TMP, stop acyclovir
C. Keep both
D. Keep both and add fluconazole
What should you do with his SMZ-TMP and acyclovir?

A. Discontinue both agents
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C. Keep both
D. Keep both and add fluconazole
Agents With Unique Considerations
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  - CD4+ helper T cells
  - Pneumocystis jirovecii (PJP)

**Complement**
- Encapsulated bacteria

---

Eculizumab (Soliris©)

- **Mechanism of action**: high affinity to complement protein C5
- **Black box warning**: meningococcal infections
  - 1000-2000 fold increase in meningococcal infection risk
- **Manufacturer Recommendation**: Provide meningococcal vaccines (MenACWY, MenB) 2 weeks prior to starting therapy
  - If unable to wait two weeks:
    - Administer vaccines ASAP and provide 2 weeks of antibacterial prophylaxis (ciprofloxacin or penicillin VK)
Need for Antibacterial Prophylaxis Throughout Eculizumab Therapy

- 80% of eculizumab-treated meningococcal cases had non-groupable N.meningitidis strains\(^1\)
  - Strains possibly not covered by vaccines\(^1\)
- Cases reports of fully vaccinated pts with serogroup B meningitis\(^2\)
- Consider prophylaxis with penicillin while on treatment\(^2\)

Alemtuzumab (Campath©)

- Mechanism: binds to CD52 on surface of B and T lymphocytes, monocytes, macrophages and natural killer cells
- 18% of patients in approval study had fatal infections (on prophylaxis)

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td>HSV: Yes</td>
<td>&gt;2 months after completion &amp; CD4+&gt;200 cells/mcL</td>
</tr>
<tr>
<td></td>
<td>CMV: weekly surveillance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HBV: if positive</td>
<td></td>
</tr>
<tr>
<td>PJP</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Bacterial</td>
<td>No recommendation</td>
<td></td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

True or False: there is some evidence that SMZ-TMP may have value throughout eculizumab therapy
True or **False**: there is some evidence that SMZ-TMP may have value throughout eculizumab therapy
Summary

• Prolonged neutropenia generally necessitates antibacterial, antifungal and antiviral prophylaxis and is most common in acute leukemia patients

• Steroids and T-cell depleting agents, such as alemtuzumab, increase risk of PJP

• Assessment of oncology drug interactions, hepatic/renal function, and risk of myelosuppression is key to regimen selection

• Alemtuzumab and eculizumab are two agents with unique antimicrobial prophylaxis considerations
## Fungal Spectrum vs Cost

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost Per Day ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>28.64</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>62.54</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>90.56</td>
</tr>
<tr>
<td>Isavuconazonium sulfate/isavuconazole</td>
<td>209.58</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>234.96</td>
</tr>
<tr>
<td>Echinocandins (micafungin &amp; caspofungin &amp; anidulafungin)</td>
<td>Caspo: 112.80 Mica: 112.20 Ani: 216</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>3262.27 weekly (466 daily)</td>
</tr>
</tbody>
</table>
## Common Viral Pathogens of Concern

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Percent of Patients Seropositive</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV- Herpes Simplex Virus</td>
<td>HSV-1: 53.9% in 14-49 year olds</td>
<td>Skin lesions, meningitis, blindness, encephalitis</td>
</tr>
<tr>
<td></td>
<td>HSV-2: 15.7% in 14-49 year olds</td>
<td></td>
</tr>
<tr>
<td>VZV- Varicella Zoster Virus</td>
<td>98% in 20-49 year olds</td>
<td>Rash, neuritis, aseptic meningitis, encephalitis, pneumonitis, hepatitis, pancreatitis</td>
</tr>
<tr>
<td>HBV- Hepatitis B Virus</td>
<td>0.27% HBsAg+</td>
<td>Acute hepatitis, chronic liver disease, cirrhosis, and hepatocellular carcinoma</td>
</tr>
<tr>
<td>CMV- Cytomegalovirus</td>
<td>58.9% of patients &gt; 6 years</td>
<td>Colitis, hepatitis, encephalitis, peri/myocarditis, retinitis, Guillen-Barre syndrome</td>
</tr>
</tbody>
</table>