Antimicrobial Prophylaxis in Hematologic Malignancies

UTAH SOCIETY OF HEALTH-SYSTEM PHARMACISTS

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Disclosure

- Relevant Financial Conflicts of Interest
  - **CE Presenter, Melanie Hunter, PharmD:**
    - No relevant conflicts of interest exist.
  - **CE Mentor, Charlotte B Wagner, PharmD, BCOP:**
    - No relevant conflicts of interest exist.
- Off-Label Uses of Medications
  - This presentation will not include off-label uses of medications.

Pharmacist Learning Objectives

- At the conclusion of this activity, pharmacists should be able to successfully:
  - Evaluate the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology/ Infectious Disease Society of America (ASCO/IDSA), and the American Society of Bone Marrow Transplantation (ASBMT) guidelines for antimicrobial prophylaxis
  - Design prophylactic regimens based on patient specific factors
  - Identify clinical challenges regarding concomitant antifungal prophylaxis and newer targeted agents

Technician Learning Objectives

- At the conclusion of this activity, technicians should be able to successfully:
  - Review the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology/ Infectious Disease Society of America (ASCO/IDSA), and the American Society of Bone Marrow Transplantation (ASBMT) guidelines for antimicrobial prophylaxis
  - Recognize prophylactic antimicrobial agents by generic and trade names
  - Distinguish between different types of antimicrobial agents used for prophylaxis in hematologic malignancies

Abbreviations

- AML: Acute myeloid leukemia
- ANC: Absolute neutrophil count
- CMV: Cytomegalovirus
- EBV PTLD: Epstein-Barr virus-associated post-transplant lymphoproliferative disorder
- GVHD: Graft versus host disease
- HCT: Hematopoietic cell transplant
- HHV: Human herpes virus
- HSV: Herpes simplex virus
- PJP: Pneumocystis jirovecii pneumonia
- SMX/TMP: Sulfamethoxazole/trimethoprim
- VZV: Varicella zoster virus

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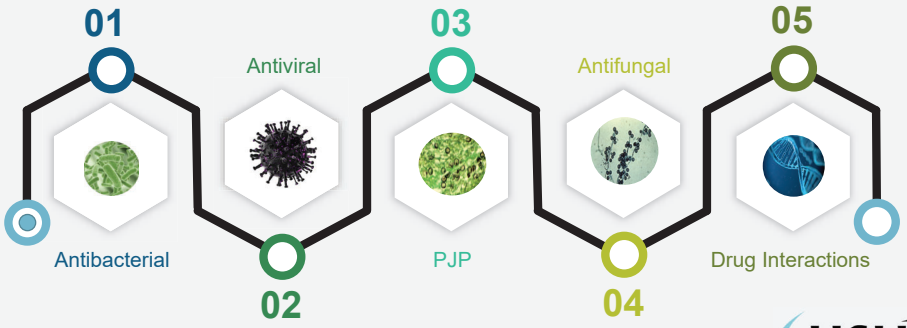
Prophylaxis Pitstops



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Background

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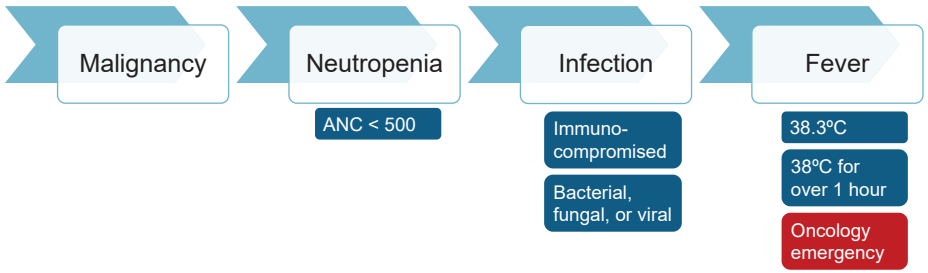
Why we use antimicrobial prophylaxis



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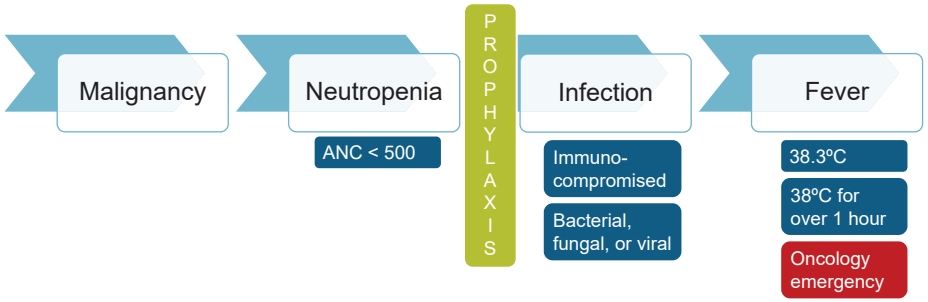
Why we use antimicrobial prophylaxis



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Determining Infection Risk

Low	Medium	High
• Neutropenia <7 days • Most solid tumors • Generally prophylaxis is not indicated	• Neutropenia 7-10 days • Lymphoma and chronic leukemia • Autologous HCT • Multiple myeloma • Purine analog therapy	• Neutropenia >10 days • Acute leukemia • Alemtuzumab therapy • Allogeneic HCT • GVHD (moderate to severe)

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Predisposing Factors for Infections

Factors	Infections

• Myelosuppressive chemotherapy
• Pre-engraftment stem cell transplant
• Central lines
• Impaired GI tract
	• Bacterial
	  • **Gram Negative**
	  • **Gram positive**
	  • **GI Strep**
	• Viral
	  • **HSV**
	  • Respiratory and enteric viruses
	  • HHV
	• Fungal
	  • *Aspergillus* species
	  • *Candida* species

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Predisposing Factors for Infections

Factors	Infections

• Post-engraftment stem cell transplant
• Alemtuzumab
	• Bacterial
	  • **Gram positive**
	  • **GI Strep**
	  • Gram Negative
	• Viral
	  • **HSV**
	  • **CMV**
	  • Respiratory and enteric viruses
	  • HHV
	  • EBV PTLD
	• Fungal
	  • *Aspergillus* species
	  • *Candida* species
	  • *Pneumocystis*

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Predisposing Factors for Infections

Factors	Infections

• Asplenia
• Hypogammaglobulinemia
• Steroids, purine analogs, alemtuzumab
• After day 100 of stem cell transplant
	• Bacterial
	  • **Encapsulated bacteria**
	• Viral
	  • **HSV**
	  • **CMV**
	  • **VZV**
	  • Respiratory and enteric viruses
	  • HHV
	  • EBV PTLD
	• Fungal
	  • *Aspergillus* species
	  • *Pneumocystis*

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Pharmacist Response Question

DM is a 45-year-old patient receiving chemotherapy prior to stem cell transplant engraftment. They have a central line placed. What viral infection are they most at risk for during this stage of treatment?

A. HSV

B. VZV

C. HIV

D. CMV

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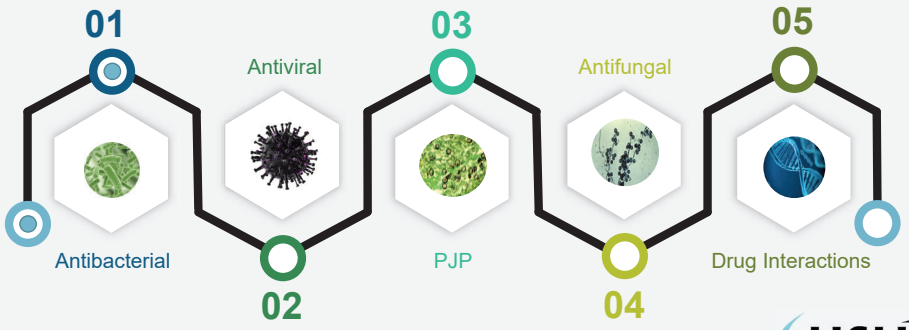
Prophylaxis Pitstops



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Antibacterial Prophylaxis

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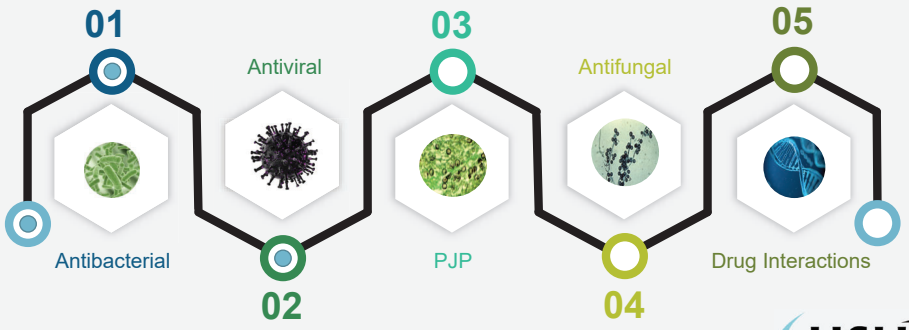
NCCN Recommendations

- Antibacterial prophylaxis is not recommended for patients with a low infection risk
- Fluoroquinolone prophylaxis is recommended for patients with intermediate or high infection risk
- Levofloxacin is the preferred antibacterial prophylaxis agent
  - SMX/TMP or an oral third-generation cephalosporin may be considered for patients who are intolerant to fluoroquinolones

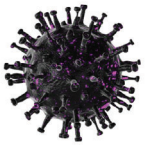
Fluoroquinolones

Trial	Population	Intervention	Results
Gafter-Gvili et al. 2005 Meta Analysis	Neutropenia Included both heme malignancies and solid tumor N=9283	Antibiotic prophylaxis v. placebo or no treatment (52 of 95 studies used fluoroquinolones)	Antibiotic prophylaxis decreased risk of death compared to placebo or no treatment (RR 0.67, 95% CI 0.55-0.81) **Fluroquinolone prophylaxis reduced all-cause mortality (RR 0.52, CI 0.35-0.77) and infection-related mortality, fever, and infections.** All antibiotics increased risk for adverse events, but the increase was not statistically significant with fluroquinolones.
Gafter-Gvili et al. 2012 Meta Analysis	Neutropenia Included both heme malignancies and solid tumor N=13,579	Antibiotic prophylaxis v. placebo or no treatment 109 trials	Antibiotic prophylaxis decreased risk of death compared to placebo or no treatment (RR 0.66, 95% CI 0.55-0.79) NNT=34 **No significant differences between quinolone and SMX/TMP prophylaxis in risk of death, but fluoroquinolones had fewer side effects and less resistance.**

Prophylaxis Pitstops



Antiviral Prophylaxis



Herpes Simplex Virus

What

- Acyclovir (Zovirax), famciclovir (Famvir), or valacyclovir (Valtrex)
- Foscarnet (Foscavir) for acyclovir-resistant HSV

When

- Neutropenia
  T-cell depletion (fludarabine, alemtuzumab, etc.)
- HCT, GVHD

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Varicella Zoster Virus

What

- Higher doses of acyclovir, famciclovir, or valacyclovir

When

- Neutropenia
  T-cell depletion (fludarabine, alemtuzumab, etc.)
- HCT
  6 to 12 months after auto-HCT
- Bortezomib
  Carfilzomib

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CMV

What

- Valganciclovir (Valcyte)
  Ganciclovir (Cytovene)
- Foscarnet
  Cidofovir
- Letermovir (Prevymis)

When

- Allogeneic HCT
- Balance duration with adverse event profiles

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Technician Response Question

Which of the following is the trade name for ganciclovir?

A. Levaquin
B. Bactrim
C. Noxafil
D. Cytovene

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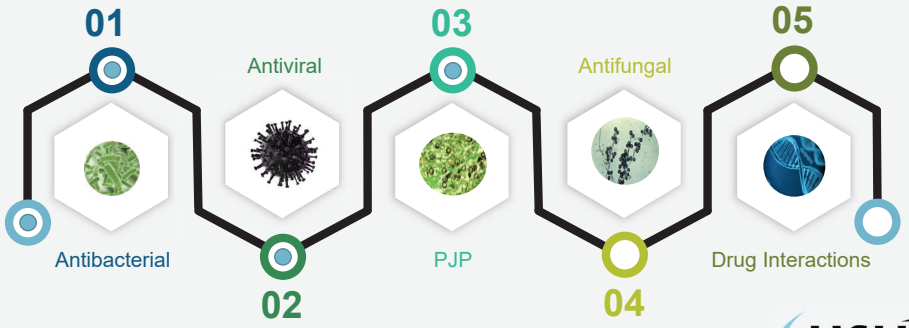
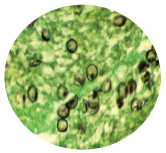
Prophylaxis Pitstops



Pneumocystis jirovecii Prophylaxis



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NCCN Guidelines

- Sulfamethoxazole/Trimethoprim (SMX/TMP) is the medication of choice for prevention of Pneumocystis jirovecii
- In cases of intolerance, SMX/TMP desensitization should be considered
- Daily dapsone, aerosolized pentamidine, or atovaquone may be considered as alternative therapies.
- IV pentamidine has been used in place of aerosolized pentamidine in many cases due to the COVID-19 pandemic.

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SMX/TMP

Trial	Population	Intervention	Results
Green et al. 2007 Meta Analysis	Patients with hematologic cancer or with a bone marrow transplant N=1245	Variety of prophylaxis regimens v. placebo or no treatment	**SMX/TMP prophylaxis regimens showed** a 91% reduction in occurrence of PCP (RR 0.09; 95% CI 0.02-0.32) and **an 83% reduction in PCP-related mortality** (RR 0.17; 95% CI 0.03-0.94) NNT=15

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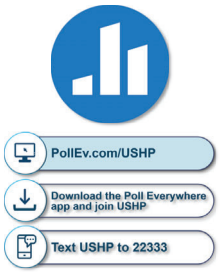
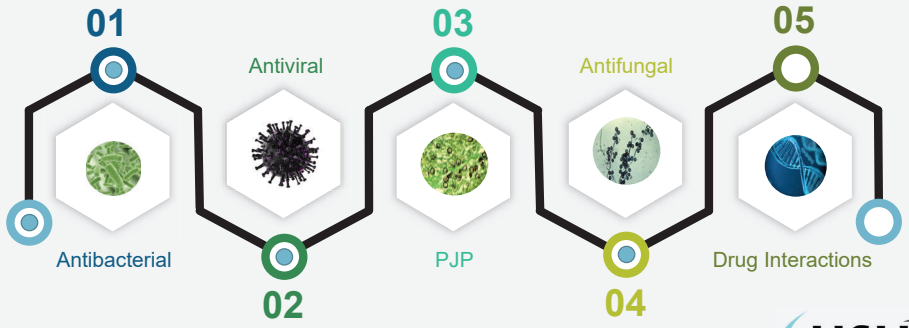
Technician Response Question



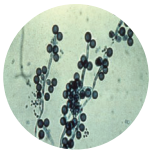
Which of the following medications can be used as an antibiotic and anti-PJP agent?

A. Levofloxacin
B. Amphotericin B
C. Posaconazole
D. Sulfamethoxazole/Trimethoprim

Prophylaxis Pitstops



Antifungal Prophylaxis



Guideline Recommendations

Auto HCT	Allo HCT	AML
• Fluconazole or micafungin • Only use antifungal prophylaxis in setting of mucositis	• Mold active agent in late stage and with GVHD • Fluconazole or micafungin should be used for at least 75 days	• Posaconazole is the drug of choice for induction • Voriconazole, fluconazole, micafungin or amphotericin B can also be considered • Risk of aspergillosis is >6%

Posaconazole

Trial	Population	Intervention	Results
Cornely et al. 2007	Patients with neutropenia resulting from chemotherapy for acute myelogenous leukemia or the myelodysplastic syndrome N=602	Posaconazole v. fluconazole or itraconazole	Posaconazole was superior to fluconazole or itraconazole in preventing invasive fungal infections (absolute reduction −6%; 95% CI −9.7 to −2.5%; P<0.001) **Posaconazole improved overall survival (P=0.04).** There were more serious adverse events in the posaconazole group.

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Pharmacist Response Question

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ST is a patient who was recently diagnosed with AML and is starting induction therapy. What antimicrobial prophylaxis would you recommend the teams starts?

A. Azithromycin, SMX/TMP, and letermovir
B. Levofloxacin, acyclovir, and posaconazole
C. SMX/TMP and amphotericin B
D. This patient does not need antimicrobial prophylaxis until their consolidation phase treatment

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Technician Response Question

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A patient needs an insurance appeal submitted for coverage of posaconazole for antifungal prophylaxis. Which guidelines could be used to support their need for this expensive medication? Select all that apply

A. NCCN Prevention and Treatment of Cancer-Related Infections
B. Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: ASCO and IDSA Clinical Practice Guideline Update
C. American Society for Blood and Marrow Transplant (ASBMT) Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients
D. Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update

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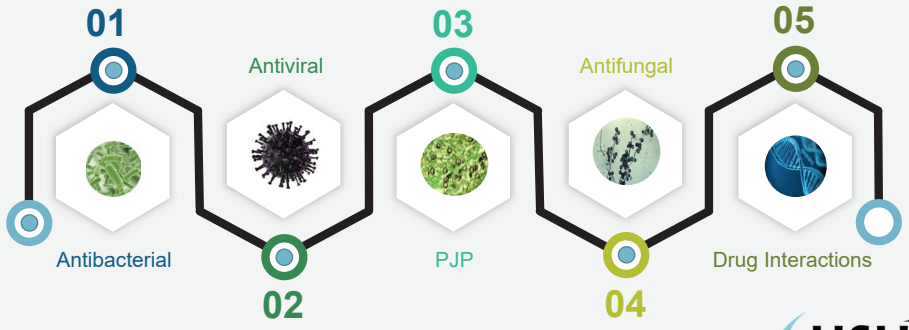
Prophylaxis Pitstops



Drug Interactions

Drug-drug Interactions

- Azoles inhibit CYP3A4 and may interact with proteasome inhibitors, tyrosine kinase inhibitors, and vinca alkaloids.
- Consider spacing these medications with the offending antifungals for 10 days.

Midostaurin

Trial	Population	Intervention	Results
Ouatas et al. 2017	Patients with newly diagnosed FLT3-mutated AML	61% of patients were using concomitant moderate to strong CYP3A4 inhibitors during induction	Shorter time to Grade III and IV adverse events No difference in complete response, progression free survival, overall survival or overall adverse events **May proceed with concomitant therapy with caution. Monitor for QTc prolongation, nausea and vomiting, and pneumonitis.**

Venetoclax

Trial	Population	Intervention	Results
Agarwal et al. 2017 drug interaction study	Adults with AML N=12	After ramp-up period, posaconazole 300 mg plus either venetoclax 50 mg or 100 mg	Venetoclax 50mg increased Cmax and AUC (53% and 76%) and venetoclax 100 mg increased Cmax and AUC (93% and 155%) Posaconazole was estimated to increase venetoclax Cmax and AUC by 7.1 and 8.8 fold, respectively. **Reduce dose by at least 75%.**

Gilteritinib

Trial	Population	Intervention	Results
CHRYSALIS drug-drug interaction study Levis et al. 2017	Adults with primary or secondary AML refractory to chemotherapy	70% of patients were using concomitant moderate to strong CYP3A4 inhibitors	Increase in gilteritinib concentrations were between 2 and 2.2 fold with moderate to strong CYP 3A4 inhibitors **May proceed with concomitant therapy with caution. Monitor for QTc prolongation.**

Pharmacist Response Question

LD is a patient on midostaurin. The provider would like to start posaconazole therapy. What would you recommend regarding the use of these medications together?

A. These medications should never be used together.
B. The midostaurin should be stopped during posaconazole therapy and resumed 3 days after posaconazole is complete.
C. Posaconazole should be used every other day rather than every day during midostaurin therapy.
D. Both medications may be used together with additional monitoring for QTc prolongation, nausea and vomiting, and pneumonitis.

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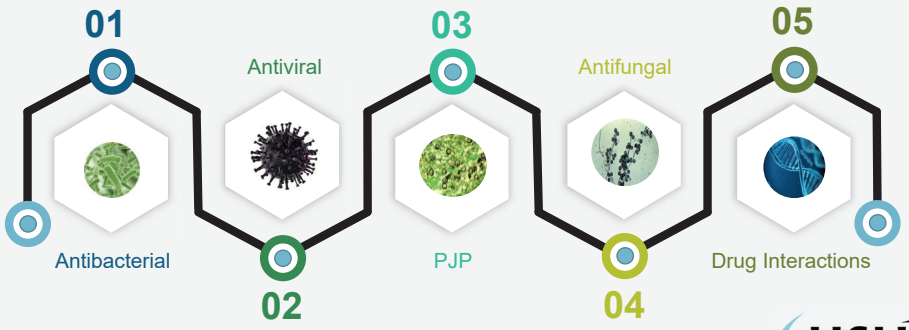
Prophylaxis Pitstops



Summary

- Antimicrobial prophylaxis helps prevent morbidity and mortality associated with neutropenic fever
- Infection risk is determined based on duration of neutropenia, type of malignancy and treatment, and patient specific factors
- Fluoroquinolones are recommended for antibacterial prophylaxis, but may also be associated with higher rates of resistant bacteria and c. diff
- Acyclovir, famciclovir, or valacyclovir are used for preventing HSV and VZV
- Valgancyclovir, ganciclovir, and letermovir are antivirals for CMV prophylaxis
- SMX/TMP is the antibacterial prophylaxis of choice for preventing PJP due to reduced mortality
- Fluconazole and micafungin are used in both auto and allo transplants
- Posaconazole prophylaxis improves overall survival in AML
- Azoles are CYP3A4 inhibitors and may interact with newer cancer therapies, requiring dose reductions or increased monitoring

Acknowledgements

- Charlotte B Wagner, PharmD, BCOP
- Brandon Tritle, PharmD, BCIDP

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