UNC Children's Clinical Practice Guideline
Antimicrobial Primary Prophylaxis for Children with Hematologic & Oncologic Malignancies

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How to use this guideline:
This document provides guidance in management of primary antimicrobial prophylaxis for children with hematologic & oncologic malignancies. This document is not intended to replace clinician judgment in individual cases; however, these guidelines should apply to most patients with such malignancies.

Population:
See **Table 1** for complete list of oncologic diagnoses covered by this guideline. The guidance provided in this document pertains to both inpatient and outpatient scenarios. For patients managed by the Pediatric Bone Marrow Transplant Service, please see their relevant infection prophylaxis policy (PolicyStat ID: 12405615).

Table 1: Summary of Antimicrobial Primary Prophylaxis (PPX) by Hematologic/Oncologic Diagnosis

Oncologic Diagnosis	Bacterial	Fungal†	Viral◊	PCP	IgG
SR B-cell ALL/LLy	–	•	–	•	•§
HR B-cell ALL or T-cell ALL/LLy	•°	•	–	•	•§
Trisomy 21 ALL	•	•	•	•	•
Infant ALL	•*	•	•	•	•
AML	•*	•	•	•	–
Relapsed or Refractory ALL/AML/LLy	•*	•	•	•	•§
New or Relapsed Hodgkin Lymphoma	–	–	–	•	–
New or Relapsed Non-Hodgkin Lymphoma	–	–	–	•	•§
Solid tumor‡	–**	–	–	•^	–

• indicates prophylaxis recommended; – indicates prophylaxis not routinely recommended; SR, standard risk; HR, high risk; ALL, acute lymphoblastic leukemia; Lly, lymphoblastic lymphoma; AML, acute myeloid leukemia
°Not all patients warrant antibacterial prophylaxis, though may be necessary during DI; see Table 2.
*May require additional Viridans Group *Streptococcus* prophylaxis; see Table 3.
**Some patients with a solid tumor may have functional or anatomical asplenia depending on tumor burden and/or resection; consider addition of penicillin prophylaxis as clinically indicated.
†Fungal prophylaxis may only be necessary during certain periods of chemotherapy; see Table 5.
◊Viral prophylaxis may only be necessary for patients meeting criteria; see Table 7.
‡In patients with stage IV neuroblastoma s/p BMT, refer to the relevant BMT infection prophylaxis policy.
^Some patients receiving low-risk chemotherapy may not need PCP prophylaxis. Refer to patient-specific protocol.
§Not all patients warrant IgG replacement; see Table 9 for further details.

Table 2. Bacterial Prophylaxis

When to start?	Begin antibacterial prophylaxis in patients receiving intensive chemotherapy expected to cause severe neutropenia (ANC < 500) for ≥7 days. °For patients with HR B-cell ALL/LLy receiving chemotherapy in delayed intensification ON AALL1732, begin antibacterial prophylaxis. Antibacterial prophylaxis is not routinely indicated during episodes of neutropenia for patients if not originally listed for prophylaxis in Table 1.	
When to stop?	Stop antibacterial prophylaxis when ANC >200 **AND** trending up. Hold antibacterial prophylaxis if patient is currently being treated for febrile neutropenia.	
Agent & Dosing	Levofloxacin	< 5 years old: 10 mg/kg/DOSE q12h (max = 500mg/DAY)
		≥ 5 years old: 10 mg/kg/DOSE q24h (max = 500mg/DAY)

Table 3. Additional Viridans Group *Streptococcus* (VGS) Prophylaxis

Indication?	The need for additional antibacterial prophylaxis beyond levofloxacin is rare; however, due to concern of invasive infections caused by VGS (e.g., *S. mitis*) that may be resistant to fluoroquinolones, addition of vancomycin as part of febrile neutropenia prophylaxis may be considered only in patients meeting the following criteria: - Patients who are currently admitted, AND - Patient history of VGS bloodstream infection, OR - Patients receiving high dose cytarabine ○ Defined as cytarabine ≥ 1000 mg/m^2/dose	
When to start?	Begin additional antibacterial prophylaxis in patients receiving intensive chemotherapy expected to cause severe neutropenia (ANC < 500) for ≥7 days. Antibacterial prophylaxis is not routinely indicated during episodes of neutropenia for patients if not originally listed for prophylaxis in **Table 1**.	
When to stop?	Stop antibacterial prophylaxis when ANC >200 **AND** trending up.	
Agent & Dosing	Vancomycin	Refer to Pediatric Vancomycin Dosing Guidelines.
		Unless otherwise stated, goal trough of 8-12 mg/L is sufficient when using intermittent infusion vancomycin (e.g., 20mg/kg/DOSE q6h)

Table 4. Additional Oral Hygiene Pharmacotherapy Prophylaxis

Indication	Proper oral hygiene may also reduce the risk of invasive infection in patients with oral mucositis caused by oral flora, including VGS. The addition of chlorhexidine gluconate and/or alkaline saline mouth rinses to standard oral hygiene (e.g., routine teeth brushing) may also reduce the risk of such infections. Consider the addition of chlorhexidine mouth rinse in patients with AML. Consider addition of alkaline saline mouth rinse in patients who are anticipated to experience oral mucositis because of chemotherapy or in those indicated to use chlorhexidine mouth rinse and unable to tolerate.	
When to start?	Begin additional oral hygiene pharmacotherapy at the start of chemotherapy anticipated to cause mucositis.	
When to stop?	Stop additional oral hygiene pharmacotherapy when ANC >200 **AND** trending up.	
Agents & Dosing	Chlorhexidine gluconate 0.12% solution	Swish & spit solution (up to 15mL) for 30 seconds twice daily after brushing; do not swallow solution.
	Alkaline saline 2% solution	Swish & spit solution (up to 10mL) for 30 seconds every two hours as needed for mucositis; OK to swallow solution.

Table 5. Fungal Prophylaxis

When & what to start based on underlying malignancy:	**SR B-cell ALL/LLy**	**When:**	Antifungal prophylaxis only indicated for induction and delayed intensification. Begin prophylaxis at start of each chemotherapy cycle.
		What:	Inpatient: micafungin Outpatient: fluconazole
	HR B-cell ALL/LLy:	**When:**	Antifungal prophylaxis only indicated for induction and delayed intensification. Begin prophylaxis at start of each chemotherapy cycle.
		What:	Inpatient: micafungin Outpatient: fluconazole
	Infant ALL & Trisomy 21 ALL	**When:**	Antifungal prophylaxis only indicated for induction, consolidation, and delayed intensification (*i.e.,* for the duration of inpatient phases of chemotherapy). Begin prophylaxis at start of each chemotherapy cycle.
		What:	Inpatient: micafungin Outpatient: no prophylaxis indicated
	AML & Relapsed or Refractory AML/LLy	**When:**	Begin prophylaxis at start of each chemotherapy cycle expected to cause severe neutropenia (ANC < 500) for ≥7 days.
		What:	Preferred: posaconazole Alternative: micafungin, in patients unable to tolerate posaconazole or unable to use posaconazole due to drug-drug interaction(s)
	Relapsed or Refractory ALL	Due to variability in risk of invasive fungal infection and chemotherapy regimens, when & what to start for this patient population will be decided on a case-by-case basis in conjunction with input from Pediatric Infectious Diseases.	
When to stop?	Stop antifungal prophylaxis when ANC >200 **AND** trending up or at discharge, whichever occurs first.		
Agents & Dosing	Fluconazole	3-4mg/kg/DOSE q24h (max = 400mg/DOSE)	
	Micafungin	1mg/kg/DOSE q24h (max = 50mg/DOSE)	
	Posaconazole	For dosing information, refer to the Azole Antifungal Therapeutic Drug Monitoring Guideline on the Pharmacy Intranet.	
		Delayed release tablets preferred over oral suspension.	
		OK to split/crush and can be administered via enteral tube.	
		Suspension must be administered with high fat meal or with a liquid fat (e.g., MCT oil, melted butter, olive oil).	

Table 6. *Pneumocystis jirovecii* Pneumonia (PJP/PCP) Prophylaxis

When to start?	All patients receiving chemotherapy should receive prophylaxis against *Pneumocystis jirovecii* pneumonia. In some patients receiving low-risk chemotherapy, PCP prophylaxis may not be indicated. Refer to patient-specific protocol for further details.
When to stop?	Continue prophylaxis until THREE months after completion of chemotherapy.
Agents & Dosing	Trimethoprim/sulfamethoxazole (TMP/SMX) preferred whenever possible. Refer to **Tables 6.1-6.2** for additional details.

Table 6.1. Dosing & Considerations for PCP prophylaxis

Preference	Agent	Dosing	Frequency
First-line	Trimethoprim/ Sulfamethoxazole	5mg TMP/kg/DAY (max = 160mg TMP/DOSE)	BID Sat/Sun
Second-line	Atovaquone	1-3 months old: 30mg/kg	Daily
		4-24 months old: 45mg/kg	
		>24 months old: 30mg/kg (max dose = 1500mg)	
	Pentamidine* (INH)	300mg	Q28 days
Third-line	Pentamidine† (IV)	4mg/kg (max = 300mg)	Q28 days
	Dapsone	2mg/kg/dose (max = 100mg)	Daily
		4mg/kg/dose (max = 200mg)	Weekly

*Use in patients <5yo should be avoided due to concern with incomplete inhalation of dose. Consider alternative agent.
†At least one retrospective study found an increased rate of breakthrough PCP in patients <2yo. Consider alternative agent.

Table 6.2. Characteristics of Alternative Drugs for PCP Prophylaxis

Characteristic	Atovaquone	Pentamidine (INH)	Pentamidine (IV)	Dapsone
Route of admin	Enteral	Inhalation	Intravenous	Enteral
Dosage form(s)	Suspension	Inhalation	Intravenous	Tablet & suspension
Administration	Daily	Q28 days	Q28 days	Daily
Age limitations	None	≥5 years*	≥2 years†	None
Requires special equipment	No	Respirgard II nebulizer & negative pressure room PolicySTAT ID: 13959686	No	No
Able to use in G6PD deficiency	Yes	Yes	Yes	No
Notable adverse effects	GI distress	Bronchospasm (pre-med w bronchodilator)	Infusion reaction (infuse over 60-120 min)	Hemolytic anemia, methemoglobinemia
Toxoplasma coverage	Yes	No	No	Yes
Cost	High	Low	Low	Low

*Use in patients <5yo should be avoided due to concern with incomplete inhalation of dose. Consider alternative agent.
†At least one retrospective study found an increased rate of breakthrough PCP in patients <2yo. Consider alternative agent.

Table 7. Viral (HSV) Prophylaxis

<table>
<tr><td>Indication?</td><td colspan="2">Herpes simplex virus 1 & 2 (HSV-1/2) prophylaxis can be considered for certain patients depending on their underlying malignancy and history of virus exposure (i.e., HSV IgG). Prophylaxis options available have activity against HSV-1/2 and VZV; however, prophylaxis specifically for VZV is not typically warranted.

While most patients may not need HSV prophylaxis, consider its use in patients who meet <u>all</u> of the following criteria:
1) HSV-1 and/or HSV-2 IgG+ (indicates exposure to HSV in past); AND
2) Infantile ALL, Trisomy 21 ALL, AML, relapsed ALL/AML/Lly, or new/relapsed mature B-cell lymphoma; AND
3) History of HSV disease prior to or during chemotherapy</td></tr>
<tr><td>When to start?</td><td colspan="2">If choosing to use HSV prophylaxis, consider starting at initiation of chemotherapy.</td></tr>
<tr><td>When to stop?</td><td colspan="2">HSV prophylaxis may be stopped at the completion of chemotherapy.</td></tr>
<tr><td rowspan="5">Agent & Dosing</td><td rowspan="2">Valacyclovir (preferred)</td><td>Enteral dosage forms: tablet (500mg, 1000mg) and oral suspension (50mg/mL; <u>not</u> commercially available, but can be compounded at UNC)</td></tr>
<tr><td>HSV Prophylaxis: 20mg/kg/DOSE q12h PO (max = 500mg/DOSE)</td></tr>
<tr><td rowspan="3">Acyclovir</td><td>Enteral dosage forms: tablet (400mg, 800mg), capsule (200mg), and oral suspension (40mg/mL; commercially available)</td></tr>
<tr><td>HSV prophylaxis: 20mg/kg/DOSE q12h PO (max = 800mg/DOSE)</td></tr>
<tr><td>If HSV prophylaxis is necessary and patient is unable to tolerate any enteral medications, acyclovir IV 5mg/kg/DOSE q8h OR 250mg/m^2/dose q8-12h may be considered.</td></tr>
</table>

Table 8. Varicella Zoster Post-Exposure Prophylaxis (VZV PEP)

Indication?	Post-exposure prophylaxis may be warranted for at-risk patients who experienced a significant exposure to varicella zoster virus (VZV). Consultation with Pediatric ID is recommended as management is patient specific. Additional information may be obtained from the AAP Red Book. Information to investigate include whether the patient has **evidence of immunity** (see definition below) as well as a **detailed account of the VZV exposure** (e.g., timing and duration of exposure, nature of index case illness [i.e., disseminated zoster, chickenpox]). **Evidence of immunity** is defined as one of the following: receipt of 2 varicella vaccine doses; laboratory evidence of immunity (i.e., positive varicella IgG); laboratory confirmation of prior wild-type disease; prior diagnosis of varicella or zoster by a health care provider. **Management options** for VZV PEP may include use of passive immunity via varicella-zoster immune globulin (VZIG, preferred) or IVIG; alternatively, chemoprophylaxis with an antiviral (i.e., valacyclovir or acyclovir) may be used. Prompt initiation of VZV PEP is necessary. Varicella vaccine (Varivax®) is a live vaccine that may be used in VZV PEP scenarios, but it is not indicated for immunocompromised patients.	
When to start?	VZIG: when indicated, administer as soon as possible within 10 days of exposure. Antiviral: when indicated, initiate as soon as possible within 7 days of exposure. IVIG: when indicated, administer as soon as possible within 10 days of exposure.	
When to stop?	VZIG & IVIG are one-time administrations when used for VZV PEP. Antiviral PEP may be continued up to 14 days after the exposure.	
Agent & Dosing	VZIG	Administered via intramuscular injection x1
		Dosing is weight-banded; consult with pharmacist.
	Valacyclovir	Enteral dosage forms: tablet (500mg, 1000mg) and oral suspension (50mg/mL; not commercially available, but can be compounded at UNC)
		VZV PEP: 20mg/kg/DOSE q8h PO (max = 1000mg/DOSE)
	Acyclovir	Enteral dosage forms: tablet (400mg, 800mg), capsule (200mg), and oral suspension (40mg/mL; commercially available)
		VZV PEP: 20mg/kg/DOSE q6h PO (max = 800mg/DOSE)
	IVIG	VZV PEP: 0.4g/kg/DOSE IV x1

Table 9. Intravenous Immunoglobulin (IVIG) Replacement

Indication?	Data evaluating the safety and efficacy of IVIG replacement in pediatric patients with hematologic malignancy is sparse; however, this practice exists with wide variability depending on the institution. Unless otherwise directed by study protocol, it is reasonable to consider monitoring IgG and providing IVIG replacement in patients who meet <u>all</u> the following criteria: 1) Any of the following conditions: infant ALL, trisomy 21 ALL, refractory and/or relapsed ALL/AML/Lly, or patients receiving B-cell depleting therapies (*i.e.*, blinatumomab, inotuzumab ozogamicin, rituximab, B-cell-directed CAR-T) 2) Serum Total IgG <400 mg/dL Of note, when IVIG is being considered for outpatient use, insurance companies often will not cover the dose unless the patient's Total IgG level is <400 mg/dL.	
Agent & Dosing	IVIG	0.4g/kg/DOSE IV

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