UNC SCHOOL OF MEDICINE

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

DEPARTMENT OF PEDIATRICS
DIVISION OF HEMATOLOGY-ONCOLOGY

CAMPUS BOX 7236
CHAPEL HILL, NC 27599-7236

T 919.966.1178
F 919.966.7629

UNC Pediatric Hematology / Oncology Clinical Guidelines

Topic: Prophylactic Antimicrobials for Children with Hematologic Malignancies

Date of Last Revision: 8th May 2020

Written by: Thomas Alexander, MD, MPH, Diana Gordon, NP, Jenna Kaplan PharmD, Lauren Garner, PharmD

**These guidelines have been developed to aid clinicians in making informed decisions about pediatric hematology and oncology patients. It is not intended to take the place of physician judgement. Recommendations may not be appropriate in all circumstances.

Summary / Recommendation:

1) All patients receiving chemotherapy should receive prophylaxis against *Pneumocystis jiroveci* pneumonia. Patients should continue prophylaxis until 3 months after completion of chemotherapy.

2) AML – Frontline
    a. Fungal Prophylaxis - Patients should receive antifungal prophylaxis during period where ANC < 500 and predicted to decrease and continued until ANC > 100 and rising.
    b. Bacterial Prophylaxis - Patients should receive antibacterial prophylaxis with levofloxacin during periods where ANC < 500 and predicted to continue falling and can be continued until ANC > 100 and rising.[1-5]

3) ALL – Frontline
    a. Fungal Prophylaxis - Patients should receive antifungal prophylaxis during induction therapy and during the first month of delayed intensification, though data is lacking.
    b. Bacterial Prophylaxis – There is currently insufficient evidence to recommend primary antibacterial prophylaxis for all patients in frontline ALL treatment.

4) ALL and AML - Relapsed
    a. Fungal Prophylaxis - Patients should receive antifungal prophylaxis throughout therapy.
    b. Bacterial Prophylaxis - Patients should receive antibacterial prophylaxis with levofloxacin during periods of neutropenia of expected duration > 5 days.[5]

5) Options for antifungal prophylaxis
    a. Posaconazole* – dosing is dependent on age and formulation used; see appendix 1
        i. First line for AML
    b. Fluconazole* – 3-4 mg/kg/day (maximum 400 mg/day) IV or PO
        i. First line for outpatient ALL
    c. Micafungin – 1 mg/kg/day (maximum 50 mg/day) IV
        i. First line for inpatient ALL
        ii. Use concomitantly with posaconazole in AML patients until posaconazole trough is therapeutic
    d. Voriconazole* – 9 mg/kg q 12hrs (maximum 300 mg q 12hrs) IV or PO
        i. Second line for AML

*Careful attention to drug-drug interactions with azoles

6) Antibacterial prophylaxis
    a. Levofloxacin
        i. Dosing for children < 5 years of age is 10 mg/kg/dose PO or IV every 12 hours
        ii. Dosing for children ≥ 5 years is 10 mg/kg/dose PO or IV once daily

Background / Data Summary:

Acute Myeloid Leukemia

There is strong support for primary prophylaxis against invasive fungal infections (IFI) for patients undergoing treatment for AML. However, the optimal antifungal agent is unclear and depend on age, drug availability, and interactions with concomitant medications. The use of primary prophylaxis for bacterial infections in AML is also no supported by literature. There is consistent evidence for patients with AML that prophylactic antibacterial regimens can reduce episode of fever / neutropenia, bacteremia, and other bacterial infections, but the survival benefit is inconsistent.[5,6] Data from an institutional study showed a benefit of vancomycin / ciprofloxicin or cefepime as primary prophylaxis, but raised concerns about the number of infection seen with resistant organisms.[2] Currently, we recommend primary prophylaxis for bacterial infections with levofloxacin for patient being treated for AML during periods of neutropenia. A COG study evaluated the safety and efficacy of levofloxacin as primary prophylaxis for patients with AML, relapsed ALL or AML, or undergoing HSCT. Preliminary results of this study show decreased rates of bacteremia in patient with frontline AML or relapse acute leukemia (22% vs 43%), providing additional support for the use of levofloxacin prophylaxis in this population.[6]

Acute Lymphoblastic Leukemia

There is limited evidence based support for antibacterial or antifungal prophylaxis for patient treated for ALL in the frontline setting. During periods of neutropenia and intensive steroids use (induction and delayed intensification), patients are at increased risk of IFI. Our group has demonstrated that fluconazole is well tolerated in combination with chemotherapy given during these phases of treatment,[7] and thus recommends fluconazole prophylaxis during these phases of treatment. Two single institutional studies have demonstrated a benefit of antibacterial prophylaxis in this setting but the absolute risk reduction is small and weighed against risk of increasing antimicrobial resistance, recent recommendation are weakly against antibacterial prophylaxis in this setting.[5,8,9]

Relapsed Acute Leukemia

Patients with relapsed acute leukemia are at high risk of IFI and bacteremia resulting from advanced disease, previous myelosuppressive therapy, and the need for intensive re-induction therapy. These patients should all be treated with prophylaxis against IFI and bacteremia through chemotherapy regimens and any times ANC<500 and not expected to rise.[5]

References:

1 Gafter-Gvili, A., Fraser, A., Paul, M. & Leibovici, L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. *Ann Intern Med* **142**, 979-995 (2005).

2 Inaba, H. *et al.* Feasibility, efficacy, and adverse effects of outpatient antibacterial prophylaxis in children with acute myeloid leukemia. *Cancer* **120**, 1985-1992, doi:10.1002/cncr.28688 (2014).

3 Lehrnbecher, T. & Sung, L. Anti-infective prophylaxis in pediatric patients with acute myeloid leukemia. *Expert Rev Hematol* **7**, 819-830, doi:10.1586/17474086.2014.965140 (2014).

4 Lingaratnam, S., Thursky, K. A. & Slavin, M. A. Fluoroquinolone prophylaxis: a word of caution. *Leuk Lymphoma* **52**, 5-6, doi:10.3109/10428194.2010.527408 (2011).

5 Lehrnbecher, T. *et al.* Guideline for Antibacterial Prophylaxis Administration in Pediatric Cancer and Hematopoietic Stem Cell Transplantation. *Clin Infect Dis*, doi:10.1093/cid/ciz1082 (2019).

6 Alexander, S. *et al.* Effect of Levofloxacin Prophylaxis on Bacteremia in Children With Acute Leukemia or Undergoing Hematopoietic Stem Cell Transplantation: A Randomized Clinical Trial. *JAMA* **320**, 995-1004, doi:10.1001/jama.2018.12512 (2018).

7 Smitherman, A. B., Faircloth, C. B., Deal, A., Troy, M. & Gold, S. H. Vincristine toxicity with co-administration of fluconazole during induction therapy for pediatric acute lymphoblastic leukemia. *Pediatr Blood Cancer* **64**, doi:10.1002/pbc.26525 (2017).

8 Sulis, M. L. *et al.* Effectiveness of antibacterial prophylaxis during induction chemotherapy in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer*, doi:10.1002/pbc.26952 (2018).

9 Wolf, J. *et al.* Levofloxacin Prophylaxis During Induction Therapy for Pediatric Acute Lymphoblastic Leukemia. *Clin Infect Dis* **65**, 1790-1798, doi:10.1093/cid/cix644 (2017).

APPENDIX 1: POSACONAZOLE PROPHYLAXIS DOSING (Target trough ≥ 700 ng/mL)

	DOSING BASED ON FORMULATION		
	IV (need loading dose) **Max: 300 mg/dose**	**Oral suspension**** **Max: 400 mg/dose**	**Delayed-release tablets* (need loading dose)**
>6 months – 2 years	10 mg/kg/dose BID on day 1 followed by 10 mg/kg/dose daily	8 mg/kg/dose TID	---
2 years – 6 years	10 mg/kg/dose BID on day 1, followed by 10 mg/kg/dose daily	8 mg/kg/dose TID	8-10 mg/kg/dose BID on day 1, followed by 8-10 mg/kg/dose daily
7-12 years	6-8 mg/kg/dose BID on day 1, followed by 6-8 mg/kg/dose daily	6 mg/kg/dose TID	8-10 mg/kg/dose BID on day 1, followed by 8-10 mg/kg/dose daily
> 12 years	300 mg BID on day 1, followed by 300 mg daily	4-6 mg/kg/dose TID	5-7 mg/kg/dose BID on day 1, followed by 5-7 mg/kg/dose daily OR 300 mg BID on day 1, followed by 300 mg daily

*ONLY 100 mg delayed-release tablets on UNC Hospital formulary. Cannot be crushed or cut.

** May require higher doses in this age group; would start on the higher end of the range if no baseline liver dysfunction. Must take with FAT (try butter!)