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Levofloxacin prophylaxis in pediatric oncology and hematopoietic stem cell transplantation: a literature review

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Abstract

Bloodstream infections (BSI) are one of the leading causes of morbidity and mortality in children and young adults receiving chemotherapy for malignancy or undergoing hematopoietic stem cell transplantation (HSCT). Antibiotic prophylaxis is commonly used to decrease the risk of BSI; however, antibiotics carry an inherent risk of complications. The aim of this manuscript is to review levofloxacin prophylaxis in pediatric oncology patients and HSCT recipients. We reviewed published literature on levofloxacin prophylaxis to prevent BSI in pediatric oncology patients and HSCT recipients. Nine manuscripts were identified. The use of levofloxacin is indicated in neutropenic children and young adults receiving intensive chemotherapy for leukemia or undergoing HSCT. These results support the efficacy of levofloxacin in pediatric patients with leukemia receiving intensive chemotherapy and should be considered in pediatric patients undergoing HSCT prior to engraftment.

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Keywords

Blood stream infection; levofloxacin; pediatric bone marrow transplant; pediatric cancer; prophylaxis

Introduction

Bloodstream infections (BSI) are one of the leading causes of morbidity and mortality in pediatric oncology patients receiving intensive chemotherapy and undergoing hematopoietic stem cell transplantation (HSCT).[1–3] Bacterial BSIs (BBSIs) have been reported in up to 66% of pediatric oncology and HSCT patients.[4] Well-documented risk factors for BSIs in this patient population include the presence of a central venous catheter (CVC), high-dose chemotherapy, extended periods of neutropenia, graft-vs-host disease (GVHD), and mucosal barrier injury.[5–8] Specifically, in adult HSCT recipients (age >18 years old), risk factors for BSIs include the use of unrelated graft sources, myeloablative conditioning regimens, acute GVHD, mucositis, transplant-associated thrombotic microangiopathy (TA-TMA), primary malignant disease, andsteroiduse.[6,9] In multivariate analysis, pre-engraftmentBSIhasbeenassociatedwithengraftmentfailureandhig h-riskdiseasestatusatthetimeofHSCT.[10]

Prior large studies in adult oncology patients receiving myelosuppressive chemotherapy demonstrated levofloxacin prophylaxis diminished the incidence of fever, probable infection, and hospitalization and showed beneficial impacts on mortality.[11,12] In comparison, studies evaluating trimethoprim-sulfamethoxazole, erythromycin, and amoxicillin-clavulanate prophylaxis show no clear overall benefit.[13–15] In contrast, early studies using fluoroquinolone prophylaxis in pediatric acute leukemia patients reduced hospitalization rates, intensive care admissions, and bacteremia rates compared to historical controls.[16,17]

The use of prophylactic antibiotics to prevent bacterial infections has not been universally adopted for pediatric oncology and HSCT recipients. Previous clinical practice guidelines for antibacterial prophylaxis in pediatric cancer and HSCT patients only administered a weak strength of recommendation based on high-quality evidence to consider systematic antibacterial prophylaxis in children with acute myelogenous leukemia (AML) and relapsed acute lymphoblastic leukemia (ALL). For autologous HSCT (auto-HSCT) and allogeneic HSCT (allo-HSCT) patients, the guideline made weak recommendations against routine antibiotic prophylaxis in this patient cohort.[18] This may be secondary to the negative consequences of routine antibiotic administration, including *Clostridium difficile* (*C. difficile*)associated diarrhea, development of bacterial resistance, and antibiotic-related toxicities.

Data gathered internally for quality improvement related to levofloxacin use by the Children's Hospitals' Solutions for Patient Safety (SPS) Hematology-Oncology central line-associated bloodstream infection (CLABSI) Improvement team suggests significant practice variation.[19] In response, SPS Hematology-Oncology CLABSI leadership convened to conduct a literature review and synthesis to promote evidence-based standards. The

objective of this manuscript is to provide a comprehensive summary of the current published data on levofloxacin prophylaxis in pediatric oncology patients and HSCT recipients.

Materials and methods

To conduct this review, a literature search using PubMed and Google Scholar was conducted on August 4, 2022, and updated on December 31, 2022, using the following search terms: “acute leukemia,” “pediatric,” “bone marrow transplant,” “hematopoietic stem cell transplantation,” “bacterial bloodstream infection,” “bone marrow transplant,” “fluoroquinolone,” “levofloxacin,” “prophylaxis.” No filters or publication time limits were applied to the search. Only studies that included children <18 years of age were included. This resulted in a total of 11 pediatric-focused studies. Because of this review’s specific focus, studies were excluded if levofloxacin prophylaxis was not explicitly studied; specifically, if the study focused only on other antibiotics and/or fluoroquinolone prophylaxis, these studies were excluded. All search results were imported to the EndNoteX9.0 reference manager, and all duplicates were removed.

Two reviewers screened each record; each report was retrieved, and no automation tools were used. The data obtained from each report included the number of patients enrolled in levofloxacin prophylaxis-focused studies, the age of the patient populations, and study outcomes, including bacterial BSI rate.

Results

Levofloxacin spectrum of antibacterial activity

Levofloxacin belongs to the fluoroquinolone family of antibiotics. Other fluoroquinolones in this class include ciprofloxacin, moxifloxacin, and gemifloxacin. Fluoroquinolones are highly active against Gram-positive and Gram-negative pathogens.[20] Levofloxacin has increased activity against many respiratory pathogens, including *Streptococcus pneumoniae, Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae.*[20] Levofloxacin also has documented activity against some of the most common gram-positive organisms isolated from patients with hematologic malignancies, including coagulase-negative staphylococci, *Staphylococcus* aureus, and enterococci.[21] The recommendations are not to use fluoroquinolones as first-line agents in children younger than 18, except when specific indications exist.

Associated toxicities with levofloxacin

Fluoroquinolones are generally well-tolerated. However, side effects and risks associated with this class of antibiotics can include transient arthralgias, tendinopathies, QTc interval prolongation, central nervous system toxicities, thrombocytopenia, hepatic dysfunction, renal dysfunction, and *C. difficile* disease.[22] Additionally, although antibiotic prophylaxis can reduce the risk of serious infections in these immunocompromised patients, barriers to universal implementation have included the contribution toward breeding antibiotic resistance. Prior studies have analyzed stool samples with metagenomic sequencing from newly diagnosed pediatric patients being treated for ALL who received either levofloxacin or no antibacterial prophylaxis. The sequencing data showed there was an increase

in the relative abundance of trimethoprim-sulfamethoxazole resistance genes (estimated mean fold change 5.9, 95% CI 3.6–9.6%, $p < 0.0001$), but this was not changed by levofloxacin prophylaxis ($p = 0.46$). However, the predominance of topoisomerase point mutations did increase over the course of induction chemotherapy in ALL patients who received levofloxacin prophylaxis (mean prevalence 10.4%, 95% CI 3.2–25.4) compared to baseline prior to the start of chemotherapy (mean prevalence 3.7%, 95% CI 0.2–22.5). No changes were observed in the gene expression of aminoglycoside, β-lactam, vancomycin, or multidrug resistance genes in the levofloxacin and no prophylaxis groups.[23]

Outcomes in HSCT patients who develop bloodstream infections

BSI alone is a significant independent predictor of treatment-related mortality (TRM). Poutsiaka *et al.* described increased TRM (HR 1.79, 95% CI 1.18–2.73, $p = 0.007$) after adjusting acute GVHD and allo-HSCT, with both predicting death three months after HSCT. In addition, they found that bacteremia with gram-negative rods (GNR) and vancomycin-resistant enterococcus (VRE) were significantly associated with increased mortality.[24] Liu e*t al.* confirmed the negative impact of BSI on 6-month survival post-HSCT and demonstrated that patients who developed BSI had an increased length of hospital stay (LOS).[25] In a retrospective analysis, Dandoy *et al.* studied outcomes from 170 BSIs diagnosed in 100 (27%) of 374 pediatric patients undergoing HSCT.[6] They showed that BSIs were associated with increased morbidity and mortality. Specifically, one-year non-relapse mortality (NRM) was significantly increased in patients with one (20/58, 34%) and more than one (17/30, 56%) BSI in the first year post-HSCT compared with those who did not develop BSI (27/194, 14%) ($p = <0.0001$). In addition, an increased risk of one-year NRM was noted in patients with at least one mucosal barrier injury laboratory-confirmed bloodstream infection (MBI-LCBI, OR 1.94, $p = 0.018$) and at least one secondary BSI (OR 2.87, $p = 0.0023$) but not in patients with CLABSI (OR 1.17, $p = 0.68$)[6] Levinson *et al.* showed that in addition to increased NRM, patients who developed early BSI during the conditioning regimen and within ten days after HSCT (and prior to engraftment) had a two-fold increased risk of developing acute GVHD.[26] These results demonstrate BSI is associated with significant harm to HSCT patients, increase the risk for adverse outcomes such as GVHD, prolong hospitalization, and increase hospital resource utilization.

Early studies in adult oncology and HSCT patients using levofloxacin prophylaxis

Early studies using fluoroquinolone, specifically levofloxacin, prophylaxis in patients with cancer focused on patients who became neutropenic after receiving chemotherapy for their underlying diagnosis. Levofloxacin prophylaxis decreased gram-positive and gram-negative bacteremia incidence and reduced infection-related mortality. Conversely, as expected, these studies also showed an increased incidence of bacteremia due to fluoroquinolone-resistant strains. Additionally, studies showed a survival advantage in patients receiving levofloxacin prophylaxis despite high resistance rates among bacterial isolates.[27] Attempts to temper the emergence of resistant bacterial strains with prophylactic levofloxacin administration have included the use of a rotating schedule of various antibiotics.[28]

The use of levofloxacin prophylaxis in adult and pediatric cancer patients has largely been limited to retrospective cohort analyses until the first prospective, multicenter, double-blind,

randomized, placebo-controlled trial was conducted in Italy from 2001 to 2003[30]. In this study, 760 consecutive adult patients with acute leukemia, solid tumors, or lymphoma were randomized to receive daily oral levofloxacin or placebo. No patients undergoing HSCT were included in this study. Patients were risk stratified based on their underlying disease and expected duration of neutropenia. The primary study endpoint was fever occurrence requiring empirical antibacterial therapy during the period of neutropenia. In the study analysis, fever was evident for the period of neutropenia in 65% of patients who received levofloxacin prophylaxis compared to 85% of patients receiving placebo. More freedom from fever was observed in patients with acute leukemia, those with solid tumors, and those receiving treatment for lymphoma. Overall, the cohort who received levofloxacin had a lower incidence of bacteremias, microbiologically documented infections, and single-agent gram-negative bacteremias, especially due to *Escherichia coli*, compared to the placebo group. Medication compliance was good and similar in both the levofloxacin and placebo groups. The overall infection-related mortality rate was similar between the two groups, with 2% in the levofloxacin group and 4% in the placebo group ($p = 0.36$).[29]

Patients undergoing HSCT have more substantial hurdles as their expected risk period for bacterial infection is commonly more prolonged due to the intense myeloablative conditioning they receive and their neutrophil recovery, depending on the pace of their engraftment. For HSCT patients, prior retrospective studies have compared clinical and microbiological outcomes secondary to the impacts of changes to antibiotic prophylaxis practice. For example, in 2002, the Fred Hutchinson Cancer Research Center changed from ceftazidime to levofloxacin for antibacterial prophylaxis for adult HSCT recipients. The levofloxacin cohort (August 2002–2005) was compared to a group of historical controls who received ceftazidime for antibiotic prophylaxis from 2000 to 2002. This retrospective analysis demonstrated at day 100 from HSCT, patients receiving levofloxacin had increased rates of febrile episodes but had decreased rates of significant bacteremia compared to those receiving ceftazidime (19.2% vs. 29.6%, $p = 0.02$).[30] While overall antibiotic therapy use did not differ between the levofloxacin and ceftazidime groups, the average acquisition costs for the levofloxacin group were lower than the ceftazidime group. Furthermore, in the levofloxacin group, there was no increase in rates of isolation of more resistant bacterial strains, the incidence of *C. difficile* infection, the incidence of infection at other body sites, and survival.

Initial prospective studies have examined fluoroquinolones (ciprofloxacin) specifically for bacterial infection prophylaxis in HSCT recipients. Still, these studies were performed several decades ago and were not randomized nor placebo-controlled.[31,32] One of the first randomized, double-blinded, placebo-controlled single-center studies in HSCT recipients was conducted in Germany in 2007. However, an important difference is that patients in this study received either levofloxacin or placebo within seven days after absolute neutrophil recovery (ANC $>0.5\times10^9$/L) was achieved following HSCT. The primary aim of this study was to evaluate the incidence of infections with proven or presumed bacterial origin after neutrophil recovery in patients receiving levofloxacin prophylaxis compared to patients receiving placebo. The study enrolled only 18 adult patients, and only 13 could be analyzed with respect to the primary aim, greatly limiting the power of the final analysis. This study

demonstrated bacterial infections tended to be lower in patients receiving levofloxacin (20%) compared to placebo (50%), but this difference did not reach statistical significance.[33]

Levofloxacin prophylaxis in pediatric oncology and HSCT patients

Similar to the published literature in adult cancer and HSCT patients, early studies exclusively performed in pediatric patients were retrospective. There are few studies exclusively evaluating levofloxacin prophylaxis pediatric ALL population. Two international studies based in Saudi Arabia and Indonesia analyzed ciprofloxacin prophylaxis during different phases of ALL therapy and had conflicting results.[16,34] In one of the larger, single-center prospective cohort studies of pediatric ALL, patients who received levofloxacin prophylaxis were compared to patients who received no prophylaxis or other prophylaxis during the induction phase of therapy on the total XVI study. Patients who received levofloxacin prophylaxis had decreased odds of febrile neutropenia, bacterial infection, and bloodstream infection by ≥70%. ALL patients who received levofloxacin prophylaxis had lower odds of *C. difficile* infection and broad-spectrum treatment antibiotic exposure by >95%.[35] Additionally, a prospective study analyzing pediatric ALL patients who received either oral levofloxacin or moxifloxacin prophylaxis reported reduced bacteremia rates during induction therapy (10.9% in the prophylaxis group vs. 24.4% in the control group, $p < 0.0001$).[36]

Observational studies in pediatric ALL patients have shown no increased rates of neurotoxicity in patients receiving fluoroquinolone antibiotic prophylaxis throughout their therapy.[37] Additionally, levofloxacin has been used as a step-down method of prophylaxis in pediatric neutropenic cancer patients and found to reduce intravenous antibiotic use at home and less IV antibiotic initiations within 24 h of a new healthcare encounter up to a week from discharge.[38] Furthermore, levofloxacin prophylaxis has been found to be a cost-effective measure in pediatric acute myelogenous leukemia (AML) patients in reducing the frequency of intensive care unit (ICU) admissions and hospital costs.[39]

Exclusive analyses evaluating pediatric HSCT recipients and levofloxacin prophylaxis are rare. A single-center retrospective study based in Italy compared the outcomes of levofloxacin versus ciprofloxacin prophylaxis in allo-HSCT pediatric patients with hematologic malignancies.[40] Levofloxacin prophylaxis correlated with reduced rates of bloodstream infections compared to the ciprofloxacin group (15% vs. 28.3%, $p < 0.05$) and rates of *C. difficile* infections (2.5% vs. 15%, $p < 0.05$). There was no difference in the number of febrile neutropenia days in the levofloxacin group (33.3%) compared to the ciprofloxacin group (36.7%, $p = 0.74$). Overall mortality at 30 days and 90 days after HSCT was not different between both prophylaxis groups.

The first multicenter, open-label, randomized trial in exclusively pediatric patients (ages 6 months to 21 years old) enrolled 200 patients with acute leukemia and 424 patients undergoing HSCT to receive levofloxacin prophylaxis or placebo between September 2011 and April 2016. Patients with acute leukemia were randomized to receive levofloxacin prophylaxis or placebo during two consecutive cycles of chemotherapy. HSCT recipients were randomized to receive levofloxacin prophylaxis or placebo during a single HSCT procedure. The primary outcome measure was the occurrence of bacteremia during the

two chemotherapy cycles for acute leukemia patients or a single transplant procedure for HSCT procedures. The major findings from this study demonstrated a markedly reduced occurrence of bacteremia in acute leukemia patients in the levofloxacin prophylaxis group compared to the control group (21.9% vs. 43.4%, $p = 0.001$). This difference was not observed in the HSCT cohort, where the risk of bacteremia was similar between the levofloxacin prophylaxis group and the control groups (11.0% vs. 17.3%, $p = 0.06$). Secondary outcome measure analysis showed that all patients receiving levofloxacin prophylaxis had less fever and neutropenia (71.2% vs. 82.1%, $p = 0.002$). Additionally, there was no difference observed between the levofloxacin prophylaxis and placebo groups in risk of severe infection, invasive fungal disease, *C. difficile*-associated diarrhea, or musculoskeletal side effects.[41]

An observational study of 96 pediatric patients undergoing auto-HSCT compared patients who received levofloxacin prophylaxis to historical controls. Their main observations included a delay in time until the onset of the first fever in the levofloxacin cohort (median of 15 days) compared to historical controls (median of 11 days). Infectious complications were also higher in the historical controls compared to patients who received levofloxacin prophylaxis.[42] Risk factors for breakthrough bacteremia on antibiotic prophylaxis with ciprofloxacin have included serotherapy with anti-thymocyte globulin and cord blood as stem cell sources.[43]

An international and multidisciplinary panel convened to publish a series of clinical practice guidelines for the use of antibacterial prophylaxis administration in pediatric cancer and HSCT patients.[18] Based on this expert panel of recommendations, it was strongly recommended that systemic antibacterial prophylaxis for children should not be extended to patients whose therapy is not expected to result in severe neutropenia (ANC $<0.5 \times 10^9$/L) for at least seven days. And if systemic antibacterial prophylaxis is planned, the preferred agent administered should be levofloxacin because of the recent data published on children and its microbiological spectrum of activity. We have summarized the key pertinent literature in Table 1.

Bacterial resistance with levofloxacin prophylaxis

One of the major concerns related to the use of antibiotics, specifically fluoroquinolone, prophylaxis is the emergence of multi-drug resistant organisms (MDRO) that are more difficult to treat. MDROs are defined as bacterial isolates that belong to one of the following categories: VRE, methicillin-resistant *Staphylococcus aureus* (MRSA), or multidrug-resistant gram-negative bacteria (MRGN), as described previously.[48]

The gut flora contains collections of antibiotic-resistance genes, collectively called the gastrointestinal resistome, which serve as a source of potential antibiotic resistance for bacteria.[49] Margolis et al. evaluated the impact of levofloxacin prophylaxis on antibiotic resistance genes by comparing the gastrointestinal microbiome in fecal samples from pediatric ALL patients who received Levaquin prophylaxis ($n = 31$) and those who did not ($n = 18$). They found an increase in the prevalence of topoisomerase point mutations in the levofloxacin cohort (mean prevalence was 3.7% [95% CI 0.2–22.5] at baseline vs. 10.4% [3.2–25.4] after induction therapy) versus those not receiving levofloxacin was 0%

at baseline and 0%after induction therapy ($p < 0.0001$). They did not find evidence of cross-class resistance to other antibiotics in the fluoroquinolone prophylaxis cohort.[23]

Bloodstream infections with VRE are emerging in pediatric and adult HSCT recipients.[50] In a single-center report, the rate of VRE was substantially higher for adult patients than pediatric patients; and VREBSI resulted in inferior one-year OSpost-HSCT[47]. In addition, patients with VRE BSI have a significantly longer inpatient duration (attributable difference 2.1 days longer) and hospitalization costs.[51] *Enterococcus faecium* has emerged as a leading cause of multiple-drug resistant enterococcal infection in the United States;[52] as VRE is responsible for nearly 18% of all invasive enterococcal infections in North America, with an incidencenearlydoublinginrecentyears.[52] Notably, *E. faecium* is intrinsically more antibiotic-resistant than *E. faecalis*, with more than half of its pathogenic isolates expressing resistance to vancomycin and ampicillin. As a result, treating infections caused by this species can be difficult.[53] The primary mode of spread of VRE from patient-to-patient occurs through the hands of healthcare workers. *Enterococci* can persist for as long as 60 minutes after inoculation onto hands and last as long as four months on inanimate surfaces, where they can serve as a reservoir for ongoing transmission in the absence of regular econtamination.[54,55] Antibiotic therapy leading to VREGI overgrowth may lead to unique pathogenesis and predisposition to gut translocation and bacteremia.[56,57] Specifically, perturbation of normal commensal intestinal microbiota by antibiotics and domination by VRE was shown to precede VRE-BSI in allo-HSCT patients.[57]

MRSA produces virulent biofilms on invasive, foreign devices like endotracheal tubes and endovascular catheters.[58,59] Biofilm facilitates MRSA survival and multiplication, prolonging the organism's exposure to antibiotics as well as promoting the transfer of antibiotic resistance genes among strains.[60] The use of antibiotics, particularly cephalosporins and fluoroquinolones, strongly correlates with MRSA colonization and infection. In 2007, Shaw etal. evaluated the frequency and outcome of patients who developed MRSA BSI over a 5-year period. The frequency of MRSA infections in autologous, MSD, and MUD transplants was 3, 6, and 9%, respectively. In 7% of the infections, MRSA was directly implicated inpatient mortality.[61]

Multi-drug resistant bacterial strains are defined by their resistance to three or more antibiotic classes: carbapenems (imipenem, meropenem); penicillin (piperacillin, ticarcillin, and piperacillin–tazobactam); cephalosporins (ceftazidime, cefepime); monobactams; aminoglycosides and fluoroquinolones. In the aforementioned 2014 European survey, the median reported rates of extended-spectrum beta-lactamase (ESBL)-producing gram-negative bacilli (GNB, 15–24%), aminoglycoside-resistant GNB (5–14%), and carbapenem-resistant *P. aeruginosa* (5–14%) were substantial.[62] Consistent with the European survey, a recent study reported a 17.5% ESBL gram-negative colonization rate among HSCT patients in Germany, with only 2% of colonized patients developing bacteremia.[63] In a 2015 report from MD Anderson Cancer Center,[64] rates of stool colonization with multidrug-resistant *Pseudomonas* were 1.2% (12/794); however, seven (58%, 7/12) of the colonized patients went on to develop MDR *Pseudomonas* BSI. Differences in geography, infection control, and antibiotic stewardship likely contribute to the variable rates of these resistant pathogens.

Cost-effectiveness of levofloxacin prophylaxis in pediatric and HSCT patients

A published meta-analysis of healthcare-associated infections (HAIs) revealed that CLABSIs are associated with the highest cost of any HAI, averaging $45,814 perevent.[65] A recent evaluation in pediatric HSCT and oncology patients with ambulatory BSIs demonstrated a $40,852 median hospital charge, with the room, pharmacy, and procedure charges accounting for more than 70% oftotalcharges.[66] Finally, Wilson et al. utilized propensity scoring with matched cases while controlling for other covariates and defined the attributable cost of CLABSI to approximate $70,000 per BSI event in pediatric hematology oncology patients. In addition, patients with CLABSI had LOS that was 21.2 days longer than those without CLABSI ($p < 0.0001$).[67]

Additionally, a retrospective cohort analysis using data from the Pediatric Health Information System (PHIS) database evaluated the cost-effectiveness of levofloxacin prophylaxis compared to no prophylaxis in pediatric patients aged 0–21 years with AML during a single chemotherapy cycle. Their findings showed levofloxacin prophylaxis decreased the absolute risk of bacteremia by 17% and cost by $1464 compared to no prophylaxis—costing $8491 per bacteremia episode avoided. This is cost-effective, as an episode of bacteremia added an average of $119,478 to the encounter costs. Prophylaxis decreased absolute ICU admission risk by 2.1% costing $81,609 per ICU admission avoided. Finally, levofloxacin prophylaxis decreased absolute mortality risk by 0.7% and cost $220,457 per death avoided.[39]

Recommendations

These results support the effectiveness of levofloxacin in children and young adults with leukemia receiving intensive chemotherapy for treatment. In addition, patients undergoing HSCT may benefit from levofloxacin prophylaxis prior to engraftment. Further clinical trials are needed to determine the effectiveness of levofloxacin in reducing infection in other populations, including children with neuroblastoma or receiving therapy for sarcomas. A proposed algorithm outlining the recommended use of levofloxacin prophylaxis in pediatric oncology and HSCT patients is shown in Figure 1.

The authors recommend levofloxacin prophylaxis for pediatric acute lymphoblastic leukemia, acute myeloid leukemia, and stem cell transplant recipients while neutropenic. Patients with underlying tendinopathy or cardiac arrhythmias should avoid levofloxacin prophylaxis. Clinicians should consider the risks and benefits of levofloxacin prophylaxis in patients with neuropathy.

While levofloxacin prophylaxis is associated with decreased infections, its use comes at a cost. The main concern over the use of prophylactic antibiotics is the emergence of antibiotic resistance. Quinolone use has been associated with multi-drug-resistant *Staphylococcus aureus*, multidrug-resistant *Escherichia coli* and *Pseudomonas aeruginosa*. Institutional infection prevention programs should be aware of system-wide prophylaxis use and monitor for the incidence and occurrence of multidrug-resistant organisms.

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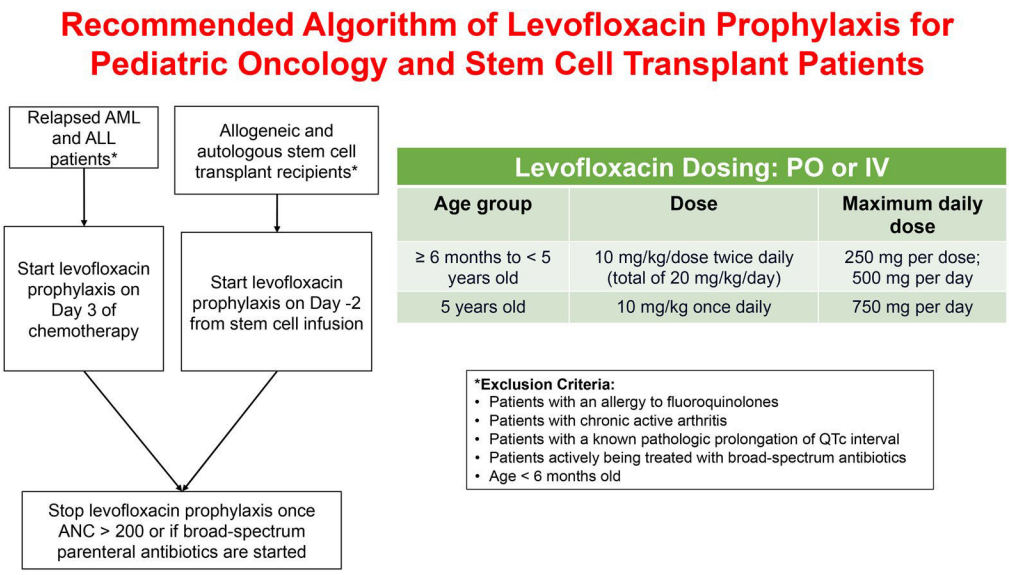

Figure 1.

Proposed algorithm of levofloxacin prophylaxis for pediatric oncology patients and stem cell transplant patients.

Table 1.

Studies on levofloxacin prophylaxis in pediatric oncology patients or undergoing hematopoietic stem cell transplant.

Study and Year	Study Design	Diagnosis	Age range	Number of patients enrolled	Main effects of levofloxacin prophylaxis
Wolf J et al., 2017[35]	Single-institutional, observational cohort study	ALL	0–12 years	344	Bacteremia • Decreased rates of bloodstream infections in levofloxacin prophylaxis group OR 0.42 (95% CI 0.15–1.16, $p = 0.09$) Fever and neutropenia • No difference in rates of febrile neutropenia with levofloxacin prophylaxis OR 0.1.17 (95% CI 0.64–2.14, $p = 0.60$) Levofloxacin-associated toxicities • Reduced rates of C. difficile infections in levofloxacin prophylaxis group OR 0.04 (95% CI <0.01–0.36, $p < 0.001$) Antibiotic exposure • Antibiotic exposure and cumulative antibiotic exposure were significantly greater in patients receiving levofloxacin or other prophylaxis than in those receiving no prophylaxis ($p < 0.001$ for all comparisons) • Levofloxacin prophylaxis did reduce exposure to cefepime/ceftazidime, vancomycin, meropenem ($p < 0.001$) and aminoglycosides ($p = 0.002$)
Sulis et al., 2018[36]	Single-institution, prospective study	ALL	1–21 years	1,024	Bacteremia • Lower rates of bacteremia in prophylaxis group treated on the DFFCI 11–001 protocol compared to the control group treated on the DFCI 05–001 protocol (10.9% vs 24.4%, $p < 0.0001$) Survival • No difference in rates of death during induction between prophylaxis group and control group (0.9% vs 2%)
Karol SE, et al., 2020[37]	Single-institutional, observational cohort study	ALL	0–18 years	598	Levofloxacin-associated toxicities • Fluoroquinolone prophylaxis during induction therapy for ALL did not increase the risk of peripheral neurotoxicity in children receiving vincristine during continuation - Any neuropathic pain (Grade 2+) HR 0.75, 95% CI 0.52–1.02 - Any neuropathy (Grade 2+) HR 0.92, 95% CI 0.39–1.82 - Any neuropathic pain or neuropathy (Grade 2+) HR 0.75, 95% CI 0.54–1.04 • High-grade neuropathic pain or neuropathy (Grade 3+) HR 1.06, 95% CI 0.51–2.22
McCormick et al. 2020[39]	Retrospective cohort cost-effectiveness analysis study	AML	0–21 years	2,601	Bacteremia cost analysis • Prophylaxis cost $8,491 per bacteremia episode prevented compared with an average added hospital cost of $119,478 Survival cost analysis • Prophylaxis cost $220,457 per death avoided. In sensitivity analysis, at a wiIingness-to-pay threshold of $100,000 per bacteremia episode avoided, prophylaxis remained cost-effective in 95% of simulations ICU[†] cost analysis • Prophylaxis cost $81,609 per ICU admission avoided, compared with an average added hospital cost of $94,181
Servidio AG et al., 2021[40]	Single-institution, retrospective cohort study	HSCT recipients with hematologic malignancies	≤13 years	180	Bacteremia • Reduced rates of bacteremia in levofloxacin group compared to the ciprofloxacin group (15% vs 28.3%, $p < 0.05$) Fever and neutropenia • Similar rates of fever and neutropenia in levofloxacin group compared to the ciprofloxacin group (33.3% vs 36.7%, $p = 0.74$) Levofloxacin-associated toxicities • Less *C. difficile* infections in levofloxacin group compared to the ciprofloxacin group (2.5% vs 15%, $p < 0.05$) Survival • Similar rates of 90-day overall mortality in levofloxacin

Study and Year	Study Design	Diagnosis	Age range	Number of patients enrolled	Main effects of levofloxacin prophylaxis
					group compared to ciprofloxacin group (8.3% vs 1%, $p = 1.0$) • Similar rates of 30-day overall mortality in levofloxacin group compared to ciprofloxacin group (1.7% vs 1.7%, $p = 1.0$)
Alexander et al., 2018[41]	Multicenter, open-label, randomized trial, patients	ALL[!], AML[@] and HSCT[#] recipients	6 months–21 years	624	Bacteremia • Acute leukemia: the likelihood of bacteremia was significantly lower in the levofloxacin prophylaxis group than in the control group (22% vs 43%; risk difference, 21.6%; 95% CI, 9%–34%, $p = .001$) • HSCT group: the risk of bacteremia was not significantly lower in the levofloxacin prophylaxis group (11% vs 17%; risk difference, 6%; 95% CI, 0.3%–13%; $p = .06$). Fever and neutropenia • Fever and neutropenia were less common in the levofloxacin group (71% vs 82%; risk difference, 11%; 95% CI, 4%–18%; $p = .002$). Levofloxacin-associated toxicities • No significant differences in C. difficile[*]-associated diarrhea (2% vs 5%; risk difference, 3%; 95% CI, −0.1% to 6%; $p = .07$) • No difference in musculoskeletal toxic effects at 2 months (11% vs 16%; risk difference, 5%; 95% CI, −2% to 11%; $p = .15$) or at 12 months (10% vs 14%; risk difference, 4%; 95% CI, −3% to 12%; $p = .28$)
Hafez et al., 2015[42]	Observational study, before-and-after study intervention analysis	Pediatric patients undergoing auto-HSCT	<18 years	96	Infection • The incidence of infectious complications was higher in patients without levofloxacin (4/46) than those with levofloxacin (1/50) Fever and neutropenia • Median duration of febrile neutropenia lower in the historical control group compared to levofloxacin prophylaxis group (11 days vs 15 days, $p \leq 0.001$) Antibiotic exposure • Median duration of empiric antibiotic use was lower in the levofloxacin group compared to the historical control cohort (10 days vs 14 days, $p < 0.001$)
Davis et al., 2022[44]	Single-institution, retrospective study with historical controls	AML, relapsed ALL	6 months–21 years	135	Bacteremia • 60% of patients in the pre-implementation group and 38% of patients in the postimplementation group developed CLABSI[%] • Reduction in gram negative rod bacteremia but observed a higher percentage of any number of levofloxacin non-susceptible GNR[^] BSI events Levofloxacin-associated toxicities • The incidence of MDRO[&] and C. difficile-associated diarrhea was similar throughout both periods Survival • Death in the post-implementation period was significantly reduced
Gardner JC et al., 2022[45]	Single-institution, retrospective study	AML, auto- or allo-HSCT recipients	Less than 21 years	60	Bacteremia • There was no difference found in the frequency of bacteremia between levofloxacin and clinician-directed prophylaxis (15.6% vs 10.4%, $p = 0.49$) Fever and neutropenia • No difference in incidence of febrile neutropenia in levofloxacin group vs clinician-directed prophylaxis group (62.5% vs 66.7%, $p = 0.70$) Levofloxacin-associated toxicities • No difference in rates of C. difficile infections in levofloxacin group vs clinician-directed prophylaxis group (12.5% vs 27.1%, $p = 0.17$) Survival • No differences in 30-day infection-related mortality between levofloxacin group and clinician-directed prophylaxis group (0% vs 2.1%, $p = 1.0$) Antibiotic exposure • Similar rates of antibiotic exposure days between both

Study and Year	Study Design	Diagnosis	Age range	Number of patients enrolled	Main effects of levofloxacin prophylaxis
					levofloxacin and clinician-directed prophylaxis groups (18.7 days vs 13.6 days, $p = 0.31$)
Margolis EB et al., 2021[46]	Prospective, single-center, cohort study	ALL	≤18 years	49	Bacteremia • No difference in bloodstream infections in no prophylaxis group vs levofloxacin group (11% vs 6%, $p = 0.62$) Fever and neutropenia • No difference in rates of febrile neutropenia in no prophylaxis group and levofloxacin prophylaxis group (67% vs 42%, $p = 0.14$) Levofloxacin-associated toxicities • Lower rates of C. difficile infection in levofloxacin group compared to no prophylaxis group (0% vs 17%, $p = 0.04$) • Increase in the prevalence of topoisomerase point mutations in the levofloxacin cohort (mean prevalence was 4% [95% CI 0.2–22.5] at baseline vs. 10% [3.2–25.4] after induction therapy) vs. those not receiving levofloxacin was 0% at baseline and 0% after induction therapy ($p < 0.0001$) Antibiotic exposure • Trend toward less antibiotic exposure days in the no prophylaxis group compared to levofloxacin group (31.7days vs 43.8days, $p = 0.09$)
Maser et al., 2020[47]	Literature review based cost-utility analysis	Relapsed ALL, AML	<21 years		Cost analysis • Levofloxacin prophylaxis produced cost savings of $542.44 compared to no prophylaxis

Abbreviations: ALL: Acute lymphoblastic leukemia

[@]AML: Acute myelogenous leukemia

[#]HSCT: Hematopoietic stem cell transplant

[%]CLABSI: Central-line associated bloodstream infection

[^]GNR: Gram-negative rod

[&]MDRO: Multidrug resistant organism

[*]*C.* difficile: *Clostridium difficile*

[†]ICU: Intensive care unit.