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Cost-Effectiveness of Levofloxacin Prophylaxis Against Bacterial Infection in Pediatric Patients With Acute Myeloid Leukemia

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Abstract

Background: Infections are the leading cause of therapy-related mortality in pediatric patients with acute myeloid leukemia (AML). While effectiveness of levofloxacin antibacterial prophylaxis in oncology patients is recognized, its cost-effectiveness is unknown. This study evaluated epidemiologic data regarding levofloxacin use and the cost-effectiveness of this strategy as the cost per bacteremia episode, intensive care unit (ICU) admission and death avoided in children with AML.

Procedure: A retrospective cohort study using the PHIS database compared demographic and clinical characteristics and receipt of levofloxacin prophylaxis in children with AML admitted for chemotherapy from January 1, 2014 through December 31, 2018. We then developed a decision analysis model in this population that compared costs associated with bacteremia, ICU admission or death secondary to bacteremia to levofloxacin prophylaxis cost from a healthcare perspective. Time horizon is one chemotherapy cycle. Probabilistic and 1-way sensitivity analyses evaluated model uncertainty.

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Contributor's Statement:

Meghan McCormick made contributions to the conception of the manuscript, developed the cost effectiveness model, analyzed and interpreted the data, drafted the initial manuscript, and reviewed and revised the manuscript for important intellectual content. Ramasubramanian Kalpatthi and Erika Friehling conceptualized and designed the study and reviewed and revised the manuscript for important intellectual content.

Nalyn Siripong analyzed and interpreted the data and revised and reviewed the manuscript for important intellectual content. Kenneth Smith made substantial contributions to the development of the cost effectiveness model, interpreted the data and reviewed and revised the manuscript for important intellectual content

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

The authors have no financial relationships relevant to this article to discuss.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Results: Prophylaxis cost \$8,491 per bacteremia episode prevented compared to an average added hospital cost of \$119,478. Prophylaxis cost \$81,609 per ICU admission avoided, compared to an average added hospital cost of \$94,181. Prophylaxis cost \$220,457 per death avoided. In sensitivity analysis, at a willingness-to-pay threshold of \$100,000 per bacteremia episode avoided, prophylaxis remained cost-effective in 94.6% of simulations. Prophylaxis use was more common in recent years, in patients with relapsed disease and with chemotherapy regimens considered more intensive.

Conclusion: Prophylaxis is cost-effective in preventing bacterial infections in patients with AML. Findings support increased use in patients considered at high-risk of bacterial infection secondary to myelosuppression.

Keywords

Acute Myeloid Leukemia; Levofloxacin; Prophylaxis; Child; Infection

Introduction

Over 40% of pediatric patients with acute myeloid leukemia (AML) experience bacterial infection as a chemotherapy complication¹. Infection-related mortality ranges from 3–8% and represents the largest cause of therapy-related mortality in this population^{2–6}. Antibacterial prophylaxis has been studied to reduce the incidence of bacterial infection in patients perceived to be at the greatest risk. Levofloxacin, a fluoroquinolone antibiotic with both gram-positive and gram-negative antimicrobial coverage, has reduced the incidence of febrile neutropenia and bacterial infections in pediatric patients receiving intensive myelosuppressive chemotherapy^{1,7}.

Accumulating evidence in favor of antibiotic prophylaxis led to the release of guidelines recommending fluoroquinolone prophylaxis in adult patients with cancer expected to have profound and protracted neutropenia related to immunosuppression⁸. Due to limited data in pediatric patients, there is only a weak recommendation for antibacterial prophylaxis in children receiving therapy for AML and relapsed acute lymphoblastic leukemia (rALL)⁹. The lack of clinical data and concerns for antimicrobial resistance and *Clostridium difficile* infection have contributed to variation in prescriber practice. A survey of infection-related supportive care practices in member institutions of the largest US pediatric cooperative trial group, the Children's Oncology Group (COG), found that antibacterial prophylaxis for pediatric patients with AML was used by only 13.3% of institutions at the time of publication¹⁰. However, the recently published results of ACCL0934, a randomized controlled trial of levofloxacin prophylaxis in pediatric patients being treated for rALL, AML and hematopoietic stem cell transplant (HSCT) conducted by the COG, has contributed compelling data regarding levofloxacin efficacy which may spur a practice change¹.

In this study, we used a multi-center inpatient pediatric database to describe current levofloxacin prophylaxis prescribing patterns in patients with AML to identify demographic and clinical factors contributing to prophylaxis use. We then used information from trials establishing the efficacy of levofloxacin prophylaxis in this setting to explore the cost-

effectiveness of prophylaxis as the cost per bacterial infection avoided, intensive care unit (ICU) admission avoided and death avoided.

Materials and Methods

Epidemiologic Study:

We conducted a retrospective cohort analysis utilizing data from the Pediatric Health Information System (PHIS) database. PHIS is an administrative database containing hospitalization data from 52 tertiary pediatric hospitals located throughout the United States (US). Discharges between January 1, 2014 and December 31, 2018 with a primary or secondary ICD-9 or ICD-10 diagnosis code for both AML and encounter for chemotherapy were included. Multiple encounters could be included for each patient if they fell within this time period. Patients were excluded at the time of HSCT or if the length of stay was less than 14 days. We compared features of patients who did and did not receive levofloxacin during admission. Levofloxacin use was identified through hospital charge codes identifying medication administration during the encounter. If at least one dose of levofloxacin was administered, patients were included in the levofloxacin cohort.

Clinical information collected from each encounter included: age at admission, gender, race, ethnicity, insurance payer, geographic region (defined by the US Census Bureau), year of admission, disease status (remission, relapse or unknown) and chemotherapeutic agents received. Variables were summarized separately for patients who received levofloxacin and those who did not. We evaluated differences in demographic variables, year of admission, disease status and chemotherapy regimen in univariate analysis by mixed effect logistic regression with random effects adjusting for clustering of encounters within patients within hospitals. Multivariable analysis with mixed effect logistic regression was utilized to assess the impact of patient age, race, ethnicity, geographic region, year of admission and chemotherapy regimen on levofloxacin use after controlling for these variables. Variables that were deemed clinically relevant or that were significantly different on univariate analyses were included in the multivariable model. All statistical analyses were completed using Stata, version 15 (College Station, TX). Tests with a two-sided p-value of 0.05 or less were considered statistically significant. This study was approved by the IRB at the University of Pittsburgh.

Decision Analysis:

We created a decision analysis model using TreeAge Pro 2019 (TreeAge Software, Williamstown, Massachusetts, USA) to evaluate the cost-effectiveness of levofloxacin prophylaxis compared to no prophylaxis in pediatric patients age 0–21 years with AML during a single chemotherapy cycle. Our analysis took a health care perspective. Outcomes of interest were the cost per bacterial infection, cost per ICU admission and cost per death avoided.

Decision Model (Figure 1):

We assumed children with AML were admitted to the hospital for chemotherapy and remained inpatient through white blood cell count nadir to recovery. Patients either received

levofloxacin prophylaxis until recovery to an absolute neutrophil count (ANC) > 500 or they did not. We assumed a dose of 500 mg twice daily, the maximum dose for prophylaxis in this setting as recommended within our institutional formulary. Prophylaxis altered the probabilities of febrile neutropenia and bacteremia but did not alter other probabilities in the model. The probabilities of ICU admission or mortality were a function of bacteremia. Our model assumed bacteremia was present only in the setting of febrile neutropenia (Figure 1). The model time horizon was one chemotherapy cycle. Content experts in pediatric oncology reviewed model creation at multiple steps to ensure face validity.

Model Parameters:

Probabilities, costs and corresponding ranges and distributions for all model parameters are listed in supplemental Table 1. We used the results of observational studies and randomized controlled trials studying levofloxacin prophylaxis in adult and pediatric patients in this setting to establish the risks of febrile neutropenia and bacteremia with and without prophylaxis^{1,2,4,7,11–17}. Published literature was used to estimate the probability of ICU admission or death, with or without bacteremia^{4,5,11,15,18–32}. The probability of levofloxacin-related adverse events was estimated using the FDA-approved package insert³³. Levofloxacin was assumed not to increase mortality.

Medication costs were obtained from the Federal Supply Schedule (FSS)³⁴. We calculated the cost of a single dose of levofloxacin administered in oral solution, tablet or intravenous form. The range of costs for one course of levofloxacin prophylaxis was obtained by multiplying the cost of levofloxacin in each formulation by the duration of neutropenia (estimated 27–38 days based on published clinical trial results)²⁵. The base case cost for each course of levofloxacin was the median value of these calculations: \$1,343 (range \$576 – 2,110). The cost of levofloxacin-related adverse events was based on incremental hospitalization costs for adverse events most commonly associated with discontinuation of levofloxacin³⁵. The added costs of a bacterial infectious complication or ICU admission were obtained from the PHIS database. We queried all encounters for pediatric patients with a primary or secondary ICD-10 diagnosis code for both AML (C92.0) and an encounter for antineoplastic chemotherapy (Z51.11) from January 1, 2018 through December 31, 2018. We calculated the difference in mean total adjusted cost of hospitalization for patients with bacterial complications (defined by ICD-10 codes for bacteremia, sepsis or central line infection) and those without, and for patients admitted to the ICU and those who were not. Total adjusted costs include all billed services adjusted for the hospital's ratio of costs to charges and cost of living within that geographic region (based on the CMS wage index).

The incremental cost-effectiveness ratio (ICER) is used in cost-effectiveness studies to compare alternative therapeutic options. The ICER is the difference in cost between two or more strategies divided by the difference in effectiveness. Its interpretation depends on the threshold chosen for comparison, where a smaller ICER indicates a more cost-effective intervention. In this study, the ICER can be interpreted as the cost per one bacteremia episode, ICU admission or death avoided. As one episode of bacteremia or one ICU admission was associated with an average increased hospitalization cost of \$119,487 or \$91,181, respectively, we selected a willingness-to-pay threshold of \$100,000 for proximity

to these values. If the cost to prevent one episode of bacteremia or one ICU admission using levofloxacin is less than the threshold value given, the intervention is considered cost-effective.

Sensitivity Analysis:

One-way and probabilistic sensitivity analyses were used to account for uncertainty in model assumptions. All parameters were varied individually in 1-way sensitivity analyses over the ranges given in supplemental Table 1 to test the influence of input values on the incremental cost-effectiveness ratio (ICER) for each outcome of interest. We then completed probabilistic sensitivity analyses for each outcome, varying all parameters simultaneously across their distributions through 1000 Monte Carlo iterations. Costs were modelled using gamma distribution functions and probabilities were modelled using beta distribution functions. Probabilistic sensitivity analysis results are reported as the percentage of iterations in which levofloxacin prophylaxis remained cost-effective at a given willingness-to-pay threshold.

Results

Epidemiologic study:

There were 1,159 patients with 2,601 admissions for chemotherapy. Levofloxacin was prescribed during 686 (26.4%) of admissions. Patients were more likely to be prescribed prophylaxis if they were older age, admitted in more recent years, receiving therapy for relapsed disease and with certain chemotherapy regimens, such as cytarabine-based regimens (Table 1). Gender and insurance payer were not included in our multivariable model as these variables were not significant in the univariate model and clinically were not expected to effect prescriber decision-making. One hundred fifty-four encounters were excluded from multivariable analysis due to missing data on ethnicity. Encounters with missing data on race were not excluded due to large numbers. Disease status was not included in multivariable analysis due to the large number of patients with unspecified disease status. Excluding patients of unspecified disease status significantly reduced the sample size, leading to model convergence issues in the mixed model setting. On multivariable analysis only year of admission remained a significant predictor of levofloxacin use, with levofloxacin being prescribed more commonly in later years.

Base-Case Analysis (Table 2):

Levofloxacin prophylaxis decreased absolute risk of bacteremia by 17% and cost by \$1,464 compared to no prophylaxis, thus costing \$8,491 per bacteremia episode avoided. This was 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. In PHIS, ICU admission was associated with an average additional hospitalization cost of \$94,181, and therefore was cost-effective. Prophylaxis decreased absolute mortality risk by 0.7% and cost \$220,457 per death avoided (Table 2)

One-Way Sensitivity Analyses (Figure 2):

Variation of model inputs for five parameters resulted in substantial changes in the incremental cost-effectiveness ratio (ICER) for cost per bacteremia episode avoided (Figure 2a). Variation in bacteremia risk with levofloxacin prophylaxis resulted in the greatest variation in results, followed by levofloxacin cost, febrile neutropenia risk with and without levofloxacin, and adverse event costs. In all cases, the ICER remained less than a willingness-to-pay threshold of \$100,000 per bacteremia episode avoided (estimated based on the added hospital costs associated with bacteremia).

In one-way sensitivity analysis for the cost per ICU admission avoided (Figure 2b), a willingness-to-pay threshold of \$100,000 per ICU admission avoided was used (based on the added hospital costs associated with admission to the ICU). In this analysis, variation in the probability of bacteremia without levofloxacin prophylaxis was the most influential parameter. Variation in bacteremia risk with and without levofloxacin, febrile neutropenia risk with and without levofloxacin, ICU admission probability with bacteremia and levofloxacin costs all resulted in an ICER that surpassed our willingness-to-pay threshold. Variation in ICU admission risk without bacteremia and the levofloxacin-related adverse event costs affected the ICER but did not surpass our willingness-to-pay threshold.

In the one-way sensitivity analysis for the cost per death avoided (Figure 2c), variation in all model inputs affected the resultant ICER except for levofloxacin-related adverse event risk. The most influential parameter was variation in the probability of febrile neutropenia without levofloxacin prophylaxis.

Probabilistic Sensitivity Analysis (Figure 3):

In the probabilistic sensitivity analysis, at the \$100,000 per bacteremia episode avoided threshold, levofloxacin prophylaxis was the preferred strategy in 94.6% of iterations (Figure 3a). At a willingness-to-pay threshold of \$100,000 per ICU admission avoided, levofloxacin was favored in 52.1% of model iterations (Figure 3b). For the cost per death avoided (Figure 3c), we used a willingness-to-pay threshold of \$400,000. This was determined using a conservative willingness-to-pay threshold of \$50,000 per quality-adjusted-life-year gained, a 5-year survival of 57% in adolescent patients with AML and an estimated survival gain of at least 15 years for long-term survivors of AML^{36–38}. At this threshold, levofloxacin prophylaxis was favored in 72.9% of iterations.

Discussion:

Survival in pediatric AML has increased dramatically over the past 30 years with a rise in survival from 20% or less in 1975 to over 60% with modern therapy³⁸. In part, this is due to increased attention to supportive care requirements during intensive myelosuppressive chemotherapy. Despite this, infection remains the largest cause of therapy-related mortality during AML treatment^{3,39}. Efficacy of antibiotic prophylaxis to prevent infection during periods of prolonged neutropenia is supported by data in the adult population⁴⁰. However, pediatric population data were scant until recently¹. Our study provides an overview of patient characteristics associated with the utilization of levofloxacin prophylaxis and how trends have been affected by recent data. We used data from the literature to support the

assertion that levofloxacin prophylaxis is also cost-effective in preventing bacterial infection, ICU admission and death.

We selected a decision-tree model over a Markov model, which simulates the transition between various health states. Markov models are utilized to describe an ongoing risk over time. Tran et al. reported up to 6.2% of pediatric patients with AML experience a second episode of bacteremia while receiving antibiotic therapy⁴². In addition, children with a history of bacteremia may be at increased risk of recurrent infection during later cycles of therapy compared to peers. Children enrolled on CCG-2891 who experienced alpha hemolytic streptococcal (AHS) infection had a 31% incidence of recurrent AHS bacteremia⁴³. The baseline risk of bacteremia also varies based on the cycle of chemotherapy being administered^{25,44,45}. However, the impact of prior levofloxacin exposure on its efficacy as prophylaxis is unknown. Sensitivity analyses evaluated how variation in the probability of bacteremia effected the cost-effectiveness of our outcome. As the risk of bacteremia without levofloxacin increases, the ICER decreases and levofloxacin use is more cost-effective. If, however, prophylaxis promotes fluoroquinolone resistance among organisms, an increased probability of bacteremia in the setting of levofloxacin may be seen and its use would be less cost-effective. As the number of chemotherapy cycles received per patient varies based on disease state (newly diagnosed AML versus relapsed disease), response to chemotherapy and cytogenetics and the probabilities associated with the scenarios above rely primarily on assumptions rather than available data, we chose to limit our model's time horizon to a single chemotherapy cycle, diminishing the usefulness of a Markov model, which typically follows patients over longer time horizons.

One of our assumptions was that patients receiving prophylaxis continued taking levofloxacin through count recovery. In reality, patients typically discontinue levofloxacin and start empiric antibiotics during febrile events. Our assumption overestimates total levofloxacin therapy costs in this patient subset and should not diminish cost-effectiveness. In ACCL0934, prophylaxis was associated with reduced febrile neutropenia¹. We did not undertake a complete economic analysis of the cost per febrile episode avoided. However, daily cost of a conventional empiric regimen with a fourth-generation cephalosporin (cefepime 2 grams every 8 hours, \$6.45/dose) and a gram-positive agent (vancomycin 1500 milligrams every 8 hours, \$17.48/dose) is \$71.79. In contrast, daily cost of levofloxacin prophylaxis (500 milligrams every 12 hours) is \$59.76, indicating levofloxacin is cost-saving³⁴.

Sensitivity analysis results exhibited the most variability with changing probabilities of febrile neutropenia and bacteremia. Published information on frequency of these events was highly variable. Infectious risk appears to be affected by chemotherapy cycle as well as whether studies considered clinically documented versus microbiologically documented infection^{2,32,43,46}. When available, we used microbiologically documented infections per cycle to estimate the probability of bacteremia. We were also limited by availability of information from pediatric-specific sources. Most sources utilized to estimate probabilities for our decision model were retrospective studies. Data from Wolf et. al was included to provide more robust evidence for levofloxacin efficacy in the pediatric population⁷. Their study population was pediatric patients with ALL in induction therapy, which accounts for

lower baseline probability of bacteremia. Only a single randomized controlled trial of levofloxacin prophylaxis has been completed in pediatric patients¹. With regards to data on cost, while hospitals costs can vary by geographic area our sample included representation from hospitals throughout the US and was adjusted for region. Hospitalization costs may also vary by treatment course, with AAML0531 reporting increased costs during Induction I and Intensification II⁴¹.

In our epidemiologic analysis the factor most closely related to the decision to prescribe prophylaxis was admission during recent years, likely attributable to accumulating data favoring antibiotic prophylaxis. Factors such as increased age and chemotherapy regimen which were associated with levofloxacin use on univariate analysis were not significant in multivariable models. There is a complex interplay between these variables. Some chemotherapy regimens, such as thioguanine, cytarabine and daunorubicin, were almost exclusively used in younger children. This corresponds with use in treating children with Down Syndrome and AML⁴⁷. Older children may be at increased risk of chemotherapy toxicity, particularly from infection-related complications and have an increased risk of relapse⁴⁸. Relapse regimens are often more intensive and can place patients at increased risk of infection⁴⁹. Lastly, chemotherapy selection is influenced by views on the current standard of care and open clinical trial protocols. AAML1031, AAML1531 and AAML1421 were open to enrollment during the study period and likely influenced the most frequently administered regimens.

Concerns regarding routine antibiotic prophylaxis include the potential for development of bacterial resistance and risks of antibiotic associated adverse effects. Alexander et. al found no significant increase in resistant stool pathogens in a subset of enrolled patients¹. However, an increase in levofloxacin resistance was observed in bacterial isolates from patients with systemic bacteremia¹. Retrospective studies of prophylaxis following HSCT report increased rates of infection with quinolone-resistant pathogens^{50,51}. A prospective study of patients with hematologic malignancies treated for neutropenic fever found levofloxacin use was associated with an increased rate of infection with fluoroquinolone-resistant organisms^{52,53}. In a meta-analysis of randomized controlled trials evaluating antibiotic prophylaxis in patients with malignancies, Egan et. al found levofloxacin prophylaxis was associated with increased risk of antibiotic resistance⁵⁴. In contrast, an earlier meta-analysis comparing fluoroquinolone prophylaxis to none, reported prophylaxis was associated with a non-significant increase in the rate of colonization, but no increase in the number of infections, secondary to resistant pathogens⁵⁵. Egan et. al noted differences in findings may be due to more strict inclusion criteria and analysis of more recently published trials in the former⁵⁴.

Multiple studies have found no increased risk in *Clostridium difficile* infection with levofloxacin prophylaxis, with some studies even noting a significant decrease in infection rates^{7,14,56}. Despite concerns regarding fluoroquinolone exposure in pediatric patients, long-term results of an observational surveillance study of over 1,000 children on Phase 3 trials found the medication was well tolerated overall. An increase in musculoskeletal adverse events was noted with levofloxacin though most cases were mild arthralgias, with no cases of tendon rupture⁵⁷.

One limitation of this study is reliance on an administrative database, which depends on accurate billing and coding. Patients in our cohort averaged 2.2 admissions per patient (range 1–7), which is fewer than the standard number of chemotherapy cycles administered with newly diagnosed AML. Contributing factors may include our requirement for an ICD code for both AML and encounter for chemotherapy to include the admission. Forty five percent of patients with a single admission were treated in either the first or last year of our inclusionary period and may have received additional cycles of therapy outside the period of data collection. In addition, patients with relapsed disease represented 24% of patients with a single admission, and often receive fewer cycles of chemotherapy to proceed quickly to HSCT.

Another limitation of the PHIS database is a lack of information from outpatient encounters. By restricting our study to encounters with length of stay beyond 14 days, we identified patients who remained in hospital following chemotherapy administration and collected data on medication administration during this period. This resulted in exclusion of patients discharged early following completion of chemotherapy who would not have had information on prophylaxis available. In AAML0531, only 11% of discharge-eligible patients were discharged early, with 8 of the 11 reviewed hospitals not discharging any patients early⁵⁸. Therefore, while we believe this strategy resulted in inclusion for the majority of children, our results may not apply to children considered at low risk of infection who would not be monitored inpatient. Several hospitals which contribute data to the PHIS database are members of the COG consortium. Patients enrolled on ACCL0934, open 2011–2016, may have been included in the data collected. These patients may not have been prescribed prophylaxis had they not enrolled on a clinical trial. We believe our cohort contributes important information from patients not represented on ACCL0934 as well as changes in prescribing practices following study closure.

In conclusion, levofloxacin prophylaxis is effective at preventing bacterial infection in pediatric patients with AML receiving intensive chemotherapy and is cost-effective. Further studies are necessary to determine how prophylaxis exposure influences efficacy and the risk of infection with resistant organisms over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations Key:

AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count

COG	Children's Oncology Group
FSS	Federal Supply Schedule
HSCT	Hematopoietic Stem Cell Transplant
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
PHIS	Pediatric Health Information System
rALL	Relapsed Acute Lymphoblastic Leukemia

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Figure 1. Decision Analysis Model.

Schematic diagram of the model. The black box represents the decision point to use levofloxacin or not. The circles represent chance nodes, with the branch selected based on the probabilities in the model. The brackets indicate the same downstream model follows both branches.

Figure 2. One-Way Sensitivity Analysis.

Variables resulting in substantial change to the ICER for (a) bacteremia episode avoided, (b) ICU admission avoided and (c) death avoided to the right of figure. Notation 'p' prior to variable signifies probability. Minimum end of sensitivity range in gray, maximum end in black. Changes in ICER associated with each end of the range in corresponding color. Vertical black bar signifies ICER from base-case analysis.

Figure 3. Probabilistic Sensitivity Analysis.

Effect of varying all parameters simultaneously on the percent of iteration in which levofloxacin is cost effective in (a) preventing bacteremia, (b) preventing ICU admission and (c) preventing death. Dashed lines indicate willingness-to-pay thresholds.

TABLE 1

Patient Data by Levofloxacin Use. Statistically significant values in bold.

	No Levofloxacin (N=1915 admissions)	Levofloxacin (N=686 admissions)	Univariate Analysis OR (95% CI)	Multivariable Analysis OR (95% CI)
Age, mean (SD), in years	7.7 (5.9)	7.9 (6.1)	1.06 (1.01–1.11)	1.05 (0.99–1.10)
Female, n (%)	911 (47.6)	332 (48.4)	0.95 (0.53–1.72)	0.94 (0.53–1.66)
Race, n (%)				
White	1243 (64.9)	406 (59.2)	Ref	Ref
Black	189 (9.9)	114 (16.6)	2.21 (0.85–5.78)	1.86 (0.73–4.71)
Other/Missing	483 (25.2)	166 (24.2)	1.18 (0.60–2.33)	1.16 (0.57–2.36)
Hispanic, n (%)	499 (26.1)	113 (16.5)	1.28 (0.74–2.21)	0.52 (0.53–1.66)
Insurance Payer, n (%)				Not Calculated
Government	976 (51.0)	326 (47.5)	Ref	
Commercial	858 (44.8)	334 (48.7)	1.48 (0.81–2.68)	
Other	81 (4.2)	26 (3.8)	2.83 (0.70–11.34)	
Geographic Region, n (%)				
Northeast	180 (9.4)	88 (12.8)	Ref	Ref
Midwest	447 (23.3)	163 (23.8)	0.61 (0.03–14.38)	0.45 (0.02–10.96)
South	619 (32.3)	247 (36.0)	2.81 (0.14–60.33)	1.80 (0.08–38.01)
West	669 (34.9)	188 (27.4)	0.98 (0.04–21.34)	0.82 (0.04–19.28)
Admission Year, n (% by year)			3.32 (2.62–4.20)	3.38 (2.63–4.35)
2013	27 (69.2)	12 (30.8)		
2014	466 (83.7)	91 (16.3)		
2015	494 (87.7)	69 (12.3)		
2016	420 (78.8)	113 (21.2)		
2017	259 (64.1)	145 (35.9)		
2018	249 (49.3)	256 (50.7)		
Disease Status, n (%)				Not Calculated
Remission	508 (26.5)	160 (23.3)	Ref	
Relapse	263 (13.7)	123 (17.9)	2.01 (1.05–3.85)	
Not Specified	1144 (59.7)	403 (58.7)	0.68 (0.41–1.15)	
Chemotherapy [*] , n (%)				
ADE	397 (20.7)	112 (16.3)	Ref	Ref
FLAG ± Anthracycline	138 (7.2)	71 (10.3)	5.38 (2.38–12.17)	2.49 (1.09–5.71)
Cytarabine±G-CSF	108 (5.6)	48 (7.0)	3.48 (1.38–8.79)	2.42 (0.95–6.18)
MidAC	410 (21.4)	131 (19.1)	1.74 (0.95–3.19)	1.86 (1.00–3.43)
Cytarabine + Etoposide	460 (24.0)	153 (22.3)	1.97 (1.09–3.54)	2.07 (1.14–3.75)
TAD	94 (4.9)	32 (4.7)	2.58 (0.83–7.98)	2.44 (0.78–7.66)
Cytarabine + Asparaginase	116 (6.1)	57 (8.3)	4.17 (1.67–10.44)	2.97 (1.20–7.37)
Other	192 (10.0)	82 (12.0)	4.82 (2.19–10.58)	3.13 (1.43–6.83)

* ADE=cytarabine, daunorubicin, etoposide; FLAG=fludarabine, cytarabine, G-CSF; MidAC=mitoxantrone, cytarabine; TAD=thioguanine, cytarabine, daunorubicin

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TABLE 2

Cost per Bacteremia Episode Avoided, ICU Admission Avoided and Death Avoided

Strategy	Cost	Patients with Bacteremia, %	Patients admitted to the ICU, %	Mortality attributed to Bacteremia, %
No Prophylaxis	\$0	26.2%	5.1%	2.0%
Levofloxacin Prophylaxis	\$1464	8.9%	3.3%	1.3%
ICER		\$8491	\$81 609	\$220 457