The Impact of a Change in Antibacterial Prophylaxis from Ceftazidime to Levofloxacin in Allogeneic Hematopoietic Cell Transplantation

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Abstract

Antibiotic prophylaxis has been utilized during the initial phases of myeloablative hematopoietic stem cell (HCT) transplantation for over two decades. However, the optimal regimen in terms of both cost and clinical effectiveness is unclear. We retrospectively compared the clinical and microbiological impact of a change in antibiotic prophylaxis practice from ceftazidime (n=216 patients with HCT in 2000 – 2002) to levofloxacin (n=219 patients, August 2002 – 2005) in patients receiving myeloablative conditioning. Levofloxacin prophylaxis was associated with fever and a change in antibiotic during neutropenia, but this strategy was not associated with any adverse outcomes. Patients receiving levofloxacin had lower rates of significant bacteremia than those receiving ceftazidime (day 100, 19.2% vs. 29.6%, p=0.02). Use of levofloxacin was associated with lower antibiotic acquisition costs. There was no deleterious impact from levofloxacin prophylaxis on survival, emergence of antibiotic resistance, detection of *Clostridium difficile* antigen in stool, incidence of viridans group streptococcal bacteremia or Pseudomonas infections. There was a trend towards lower rates of bacteruria, wound and bacterial respiratory infections in the levofloxacin than in the ceftazidime group, but these differences were not statistically significant. These data support the use of levofloxacin as prophylaxis in myeloablative allogeneic HCT when prophylaxis is employed.

Introduction

Bacterial infections are the single most common cause of infection related mortality, accounting for 36% of such deaths after allogeneic hematopoietic cell transplant (HCT) [1]. The risk of bacterial infection is largely mediated by neutropenia, defined as an absolute neutrophil count (ANC) < 500 cells/μL in blood [2,3,3]. About 20% of neutropenic cancer patients will develop an episode of bacteremia, and delayed initiation of antibiotics until an infection is documented by culture may result in excess mortality in these patients [4]. Accordingly, antibiotic prophylaxis and empirical therapy are often employed as bacterial infection risk reduction strategies. Antibiotic prophylaxis starts at the onset of neutropenia and continues until engraftment [5]. Although this approach may prevent some bacterial infections, leading to reduced mortality [6,7], the disadvantages of prophylaxis include increased antibiotic exposure with resulting higher drug costs, toxicity, and the potential for development of antibiotic resistance in bacteria. Empirical antibiotic therapy is initiated at the onset of fever in neutropenic patients. The advantage of this approach is decreased antibiotic exposure compared to the prophylaxis strategy, while the disadvantages include higher rates of infection, and the possibility that infections may advance to a critical stage before the onset of fever and the initiation of antibiotic treatment. In HCT recipients a sequential strategy is most commonly employed using antibiotic prophylaxis with onset of neutropenia, followed by a change to a different (empiric) antibiotic with onset of fever.

The Fred Hutchinson Cancer Research Center (FHCRC) has used antibiotic prophylaxis in allogeneic HCT recipients for the last 2 decades. In 2002, the FHCRC elected to transition from using ceftazidime to levofloxacin for antibacterial prophylaxis in this patient population. Ceftazidime is a third generation cephalosporin with activity against *Pseudomonas aeruginosa* and other Gram-negative rod (GNR) bacteria but with a poor Gram-positive spectrum. Levofloxacin is a fluoroquinolone with enhanced Gram-positive activity (including against *Staphylococcus aureus*) along with activity against Pseudomonas and other GNRs. The rationale underlying this transition was that levofloxacin has a broader spectrum of activity,

requires only once daily dosing of 750 mg intravenously or orally, and is significantly less expensive than 2 grams of ceftazidime administered intravenously every 8 hours. Oral levofloxacin has excellent bioavailability and is dramatically less expensive than intravenous ceftazidime for those patients who can tolerate oral medications.

The initiation of this change was associated with a mandate to monitor the outcome of this policy. In particular, we sought to determine if levofloxacin use was associated with an increased risk of GNR bacteremia due to quinolone resistant bacteria, a shift in the spectrum of bacterial pathogens causing disease, and an increased incidence of *Clostridium difficile* colitis since quinolone use is a risk factor for this infection [8]. We carried out a retrospective analysis of two consecutive treatment cohorts to compare the following outcomes during the first 100 days following transplantation: fever, failure of prophylaxis (i.e., change of antibiotic), number and types of documented bacterial infections (including bacteremias), emergence of antibiotic resistance, use of antibiotic and antifungal medications, and costs of those medications. Entry into and days spent in the intensive care unit (ICU) were assessed as surrogate markers for sepsis. Relapse and mortality in the three years following transplantation were also described.

Patients and methods

Data collection

The study population consisted of consecutively admitted adult recipients of myeloablative allogeneic HCT at the Seattle Cancer Care Alliance (SCCA) from July 2000 – December 2004, with inpatient visits at the University of Washington Medical Center and outpatient follow-up at the SCCA clinic. Patients received either ceftazidime or levofloxacin as prophylaxis during neutropenia. Pediatric patients were excluded. Ceftazidime was the standard antibacterial prophylaxis during the study period from 2000 to 2002. After August of 2002, levofloxacin prophylaxis became standard practice. Data were collected from pharmacy charts for

antibacterial and antifungal medications, and electronic medical records for fever, ANC, bacterial culture and antibiotic resistance information.

Definitions

Underlying disease was classified as advanced for all patients not in remission, patients with acute nonlymphoblastic leukemia in second or later remission, and patients with acute lymphoblastic leukemia in third remission or later. Patients with chronic myeloid leukemia were classified as having advanced disease when in blast crisis at time of transplant. All other patients were classified as not having advanced disease.

Infections were documented following standard practices at the FHCRC/SCCA. Fever was defined in this study as an oral temperature of 38.3°C or higher. Blood cultures were obtained in patients with temperatures >38.0°C, with two sets of culture bottles (aerobic, anaerobic, mycobacterial/fungal = 1 set) obtained with initial fever and then daily sets obtained with ongoing fever. Blood cultures were also obtained with hemodynamic instability, chills, and at least weekly when receiving steroids $\geq$ 0.5 mg/kg since this may mask a fever. Urine cultures were obtained with fever or urinary complaints. Clostridium difficile ELISA for common antigen and Toxin A was sent for diarrhea or fever and abdominal pain. Bronchoscopy with bronchoalveolar lavage (BAL) was obtained in patients with pulmonary infiltrates or nodules seen on radiographic images.

Bacteremic episodes were defined by any positive blood culture and summarized over two overlapping time periods: first, during the initial period of neutropenia, and second, anytime in the first 100 days after transplant. The beginning of the neutropenic period was defined by the first day after conditioning that the ANC value fell below 500, and ended with the first day that value exceeded 500. In patients with an initial neutropenic period that ended on transplant day +1 or before, infections during the second neutropenic period related to transplantation were described instead. Within each time period, additional positive cultures for the same

organism recovered within 7 days of previous positive culture were considered part of the original episode, whereas positive cultures for different organisms on different days were considered separate episodes. A polymicrobial episode was defined by positive cultures for two or more organisms on the same day. Analysis of bacteremic episodes was also performed excluding coagulase-negative staphylococci which were the most common isolates in our HCT recipients but have low pathogenic potential.

Infections identified through other sources during the first 100 days post-transplant were also summarized. Bacteruria was defined as at least 1+ growth of a pure culture; pyuria is not considered a reliable indicator of urinary tract infection in neutropenic patients and mixed bacteria on culture are associated with contamination during collection. Wound infection was microbiologically documented through biopsy of subcutaneous tissue and excluded normal flora from non-sterile sites. Respiratory tract infection was diagnosed via sputum, BAL fluid, tracheal aspirate and/or lung biopsy, with isolation of a credible pulmonary pathogen and excluding normal oral flora such as viridans streptococci, coagulase negative staphylococci, stomatococcus and diphtheroids.

Failure of prophylaxis was defined as a change in antibiotic therapy, including a discontinuation of the initial treatment and use of additional drugs. Since our description includes all further antibiotic treatment within the first 100 days post-transplant, “additional therapies” may include the original prophylaxis agent.

The burden of antibiotic use was quantified by number of “antibiotic days” during days -5 to +100 relative to transplant. An “antibiotic day” was defined as treatment with a single antibiotic on one day; one day’s treatment with two antibiotic therapies was counted as two antibiotic days, and so on. Thus, each patient’s total antibiotic days was calculated by summing up the number of days spent on each antibiotic therapy. To estimate the monetary cost of each patient’s antibiotic treatment, we considered only the price paid by the clinic to acquire the

medicines and ignored the cost of infusion. Based on common practice in our clinics, if treatment was given before day +21, we assumed that the IV cost was applicable. If given past day +21, the oral usage cost was applied. Patients with incomplete data on duration for selected antibiotics were excluded from analysis of antibiotic use and cost.

Antifungal use and cost were summarized in a similar way to antibiotics. Fluconazole is used routinely at the FHCRC/SCCA for antifungal prophylaxis in HCT. However, there is some variability in initial antifungal prophylaxis based on risk factors for mould infection. Thus, we restricted our attention to the subgroup of patients who received fluconazole as initial prophylactic therapy and described the switch to non-fluconazole (mould active) antifungal therapy after the initial transplant period. Patients with incomplete data on duration for selected antifungals were excluded from this analysis.

Statistical analysis

Patient characteristics were compared across cohorts via Chi-squared test for categorical data and t-test for continuous data. Cumulative incidence curves were used to estimate the probabilities of the time-to-event outcomes: fever, change in antibiotic regimen, bacteremia, bacteruria, wound infection, respiratory tract infection and relapse-free survival. Relapse and death in the first 100 days were treated as competing risks for all infectious disease outcomes. The statistical significance of differences in event rates was evaluated with the proportional hazards regression model. The probability of entry into the ICU was estimated using a logistic regression model. Within the subset of patients treated in the ICU, the number of days spent in the ICU was compared across cohorts via linear regression model. Factors considered as potential confounders of the relationships between the prophylactic antibiotic and the outcomes included age, sex, donor type (related vs. unrelated), receipt of total body irradiation (TBI), and cell source (peripheral blood stem cells or bone marrow). Such factors were retained in the model if their presence influenced the coefficient of interest (use of levofloxacin vs. ceftazidime)

by 10% or more. Reported p-values are two-sided, and based on the Wald statistic. No adjustments were made for multiple comparisons.

Results

The populations in the two different antibiotic prophylaxis groups were fairly similar with respect to age, diagnosis and donor type. Table 1 describes the patient characteristics by prophylaxis regimen. Significantly more patients in the ceftazidime group received bone marrow rather than a peripheral blood stem cell (PBSC) transplant, as compared to the levofloxacin group (p=0.02). There was a significantly higher proportion of men than women among levofloxacin recipients compared to ceftazidime recipients (p=0.02). The distribution of conditioning regimens varied by prophylaxis regimen, but this difference did not reach statistical significance.

Patients who received levofloxacin as their first prophylaxis regimen were significantly more likely to have a fever early after initiation of the prophylactic antibiotic, as compared to patients who initially received ceftazidime (estimates at day 30 were 69.0% (95% confidence interval (CI) 62.8 – 75.2%) and 53.7% (95% CI 47.1 – 60.4%), respectively, p=0.004 after adjustment for cell source and donor type, Figure 1). Fevers occurred at a median of 5 days (range 0 – 57 days) after initiation of the original prophylaxis regimen. Similarly, more patients receiving levofloxacin prophylaxis experienced a failure of their initial prophylaxis (p<0.001). Changes in antibiotic regimen occurred at a median of 7 days (range 1 – 24 days) after the start of the original regimen. Table 2 describes the therapies that patients received after failing initial prophylaxis.

The prophylaxis groups did not differ with regard to overall antibiotic use: the median number of antibiotic treatment days per patient was 34, range 6 – 120 days in the ceftazidime group vs. median 31, range 3 – 168 days in the levofloxacin group, based on complete data from 171 ceftazidime treated patients and 197 levofloxacin treated patients. The average antibiotic acquisition costs incorporating all antibiotics used in the study period were significantly

lower for levofloxacin than ceftazidime recipients: median $618, range $33 – 3378 vs. median $922, range $216 – 3158, respectively (p=0.001). Among the 172 ceftazidime recipients and 193 levofloxacin recipients who received fluconazole antifungal prophylaxis, there was no difference between groups in overall use of antifungals including use of mould active agents. Antifungal acquisition costs also did not vary by antibiotic prophylaxis cohort.

The probability of at least one case of bacteremia in the first 100 days after transplant did not vary by group (p=0.15). However, when single-organism coagulase-negative Staphylococcus (CoNS) infections were excluded, the levofloxacin group had a significantly lower probability of bacteremia than the ceftazidime group (p=0.02). The estimated probabilities at day 100 were 29.6% (95% CI 23.5 – 35.7%) for the ceftazidime group and 19.2% (95% CI 14.0 – 24.4%) for the levofloxacin group (Figure 2).

The spectrum of bacteria causing bacteremia was similar across groups, although the number of infections for each Gram-positive bacterium was lower in the levofloxacin cohort than the ceftazidime cohort (Table 3). The five episodes of Acinetobacter bacteremia in the levofloxacin group occurred in three subjects; two patients with one episode each and one patient with three episodes. One patient had infection with antibiotic resistant Acinetobacter in the levofloxacin cohort (Table 4).

The incidence of bacteremia in the initial post-transplant period of neutropenia did not vary by group, even when the single-organism CoNS infections were excluded. Overall, the period of neutropenia started on average at day +2, with a range from day 0 to 9; the median end time was day +17, with a range from day 2 to 37. The average duration of the initial post-transplant neutropenic period was 14 days, with a range of 1 to 34 days. There were no dramatic differences between groups in the spectrum of bacteria causing bacteremia during neutropenia.

For sources of infection other than blood, there were no significant differences between prophylaxis groups in rates of infections in the first 100 days after transplant. There was a trend

suggesting the incidence of wound infection was lower in the levofloxacin than the ceftazidime cohort, but this difference did not reach statistical significance (day 100 estimates 4.1% (95% CI 1.5 – 6.7%) and 8.8% (95% CI 5.0 – 12.6%) respectively, p=0.10). There was no difference in the probability of at least one respiratory bacterial infection episode between the cohorts (day 100 estimates 11.6% (95% CI 7.3 – 15.8%) for ceftazidime and 10.0% (95% CI 6.1 – 14.0%) for levofloxacin groups). The incidence of least one positive urine culture in the first 100 days after transplant did not differ significantly between ceftazidime and levofloxacin recipients: 22.7% (95% CI 17.1 – 28.3%) and 16.9% (95% CI 11.9 – 21.9%), respectively. However, male and female patients had significantly different experiences of this outcome: 11 of 132 (8%) men in the levofloxacin group and 2 of 107 (2%) men in the ceftazidime group had at least one positive urine culture, while 26 of 87 (30%) women in the levofloxacin group and 47 of 109 (43%) women in the ceftazidime group had at least one positive urine culture.

The probability of at least one positive blood (excluding CoNS), urine, wound, or respiratory culture in the first 100 days was estimated in order to assess the overall burden of infections. These estimates were not significantly different between prophylaxis groups (Figure 3). However, among patients with at least one infection of any type, patients in the ceftazidime group were significantly more likely than patients in the levofloxacin group to have had an infection in 2 or more sites (36% (38/107) vs. 20% (17/87), respectively, p=0.02).

There was no significant difference in rates of detection of *Clostridium difficile* either by Toxin A or common antigen in the stool between the two prophylaxis cohorts during the first 100 days after transplant. Of those subjects undergoing testing to diagnose possible *Clostridium difficile* disease, *Clostridium difficile* Toxin A was detected in 8.8% (95% CI 5.0 – 12.6%) of subjects in the ceftazidime group and 6.4% (95% CI 3.2 – 9.6%) of subjects in the levofloxacin group; *Clostridium difficile* antigen was detected in 27.8% (95% CI 21.8 – 33.8%) of subjects in the ceftazidime group and 20.1% (95% CI 14.8 – 25.4%) of subjects in the levofloxacin group. Ceftazidime recipients were more likely than levofloxacin recipients to have entered the ICU

during the first 100 days after transplant: 22% vs. 13%, p=0.03. However, the incidence of ICU treatment within the first 100 days after transplant decreased over time in the study cohort: 19% among those transplanted in 2000, 25% in 2001, 16% in 2002, 18% in 2003, and 6% in 2004 (p=0.004). Thus, the difference between prophylaxis groups may be due to advances in care in the later time period of levofloxacin use. Among those treated in the ICU, the number of days spent there did not differ between groups: median 4, range 1 – 60 days in the ceftazidime group vs. median 13, range 1 – 54 days in the levofloxacin group, p=0.42. Also, the proportion of patients who died within 100 days of transplant after treatment in the ICU did not differ between groups: 38% in the ceftazidime group vs. 46% in the levofloxacin group.

The use of levofloxacin instead of ceftazidime for prophylaxis did not adversely affect relapse-free survival (RFS). At three years post-transplant, RFS was 57.1% (95% CI 50.5 – 63.7%) in the levofloxacin group and 50.4% (95% CI 43.8 – 57.1%) in the ceftazidime group (Figure 4). After adjusting for cell source and TBI exposure, the hazard ratio of RFS for the levofloxacin group relative to the ceftazidime group was 0.81 with 95% CI 0.62 – 1.07 and p=0.13.

There were 26 deaths within 100 days of transplant in the ceftazidime group, with 14 autopsies performed and 8 documented bacterial infections contributing to death (3 *Enterococcus* species, 2 *Staphylococcus aureus*, 2 polymicrobial and 1 *Myocobacterium avium* complex). There were 26 deaths within 100 days of transplant in the levofloxacin group, with 6 autopsies performed and 7 bacterial infections documented as contributing to death (3 *Enterococcus* species including one vancomycin resistant enterococcus, 1 Acinetobacter, 1 Pseudomonas, 1 polymicrobial, and 1 with persistent CoNS bacteremia).

Discussion

Several randomized, placebo controlled trials have documented the beneficial effects of levofloxacin prophylaxis in reducing rates of fever and infection in cancer patients with

neutropenia [9,10] and reducing mortality in neutropenic patients [11,12]. Levofloxacin has several attractive characteristics including a broad spectrum of activity against Gram-negative and Gram-positive pathogens, once daily dosing, high oral bioavailability, excellent safety profile, and low cost. Some investigators have advocated caution in the adoption of levofloxacin for prophylaxis based on concerns about the potential for emergence of antibiotic resistance and a possible increase in enteric infections such as caused by *Clostridium difficile* [13]. Indeed, several studies have shown that fluoroquinolone use is a major risk factor for *C. difficile* colitis [14,15,15]. Bucaneve reported that 10 of 13 Gram-negative rods isolated from the blood of patients receiving levofloxacin prophylaxis were resistant to levofloxacin [9]. Furthermore, levofloxacin prophylaxis at 500 mg daily has been associated with an increased incidence of viridans group streptococcal bacteremia in autologous transplant recipients [16]. Recognizing the potential deleterious consequences from instituting levofloxacin prophylaxis, we sought to monitor the clinical and microbiological impact of a change from ceftazidime to levofloxacin for antibacterial prophylaxis in allogeneic HCT recipients receiving myeloablative conditioning.

Patients receiving 750 mg levofloxacin per day as prophylaxis had a significantly higher probability of developing a fever (69.0%) compared to patients receiving 2 gm ceftazidime three times daily (53.7%), though the median time to fever was the same in febrile patients (5 days). This higher incidence of fever in the levofloxacin cohort led to a higher probability of changing antibiotics (63.5%) compared to the ceftazidime cohort (45.4%), reflecting the practice of starting a different empirical antibiotic in neutropenic patients who develop a fever on prophylaxis. Patients with febrile neutropenia were most commonly switched to ceftazidime in the levofloxacin prophylaxis group, while patients in the ceftazidime prophylaxis group were most commonly switched to imipenem (Table 2). Vancomycin was used at similar rates in both groups. Despite the higher incidence of fever in the levofloxacin group, the use of mould active antifungal medications was similar between groups. Thus the lower cost of Levofloxacin

prophylaxis as well as the lower cost of Ceftazidime as initial secondary therapy over Imipenem contributed to the markedly lower total antibiotic cost that we documented in this analysis.

Ceftazidime prophylaxis resulted in a reduced rate of febrile episodes post-HCT as compared to levofloxacin prophylaxis. Interestingly, documented bacteremia (excluding CoNS which is not susceptible to levofloxacin or ceftazidime) was less frequent among patients receiving levofloxacin prophylaxis. In addition, rates of bacteruria, wound infection, isolation of a bacterial pathogen from respiratory culture, and *Clostridium difficile* antigen or toxin detection in stool were consistently lower in the levofloxacin group, although not statistically significantly different. *Clostridium difficile* toxin detection in stool provides evidence of toxigenic bacteria, whereas the antigen may be detected with either toxigenic or non-toxigenic strains of *Clostridium difficile*. Antibiotic susceptibility profiles were monitored for each bacterial isolate and there was no trend towards isolation of more resistant bacteria in the levofloxacin cohort. Three patients in the levofloxacin prophylaxis group had Acinetobacter bacteremia, an infection that was not found in the ceftazidime cohort, but these bacteria were sensitive to both levofloxacin and ceftazidime for 2 of the 3 patients (Table 4). Increased rates of Pseudomonas infection or viridans group streptococcal bacteremia did not become apparent with levofloxacin prophylaxis, despite some concerns in the literature regarding these pathogens emerging with levofloxacin use (Pseudomonas) or quinolones in general (viridans streptococci) due to suboptimal minimal inhibitory concentrations. Our use of the higher dose of levofloxacin at 750 mg daily may have mitigated these susceptibility problems. Thus, we found no evidence in our study that levofloxacin prophylaxis led to adverse consequences as reflected by the emergence of antibiotic resistance or a change in the pattern of infections.

The relapse-free survival curves were indistinguishable during the period of neutropenia when the antibiotic activity is operative, demonstrating no evidence of superiority for one prophylaxis regimen over the other. There was a trend towards better long-term relapse free survival in the levofloxacin group ($p=0.13$), but this result must be interpreted with caution

because the patients were treated with levofloxacin and ceftazidime in different time periods. Thus improvements in overall care in the later time period may account for better survival in the levofloxacin group. On the other hand, an analysis of RFS by year of transplant over the study period showed no such trend (data not shown).

There were some limitations to our study. First, this was not a randomized trial comparing two antibiotic prophylaxis regimens, but rather a retrospective analysis of two cohorts from sequential time periods. Our goal was to assess the clinical and microbiological impact of adopting levofloxacin antibiotic prophylaxis for myeloablative allogeneic transplant at one HCT center that previously used a beta-lactam antibiotic for prophylaxis. Definitive conclusions about the relative efficacy of these antibiotics would require a randomized controlled trial. We adjusted our models when appropriate for observed differences in gender and cell source between prophylaxis groups, but there may have been other factors related to changes in hospital practices over time for which we could not adjust. For example, the choice of antibiotic to be used for breakthrough fever on prophylaxis was left to the patient care teams, thus there were differences in antibiotic usage patterns within a prophylaxis group. Second, although levofloxacin resistance did not emerge as an important problem, ongoing use of an antibiotic in a community may alter the pathogens encountered on a longer time scale. Continued vigilance is necessary. Third, the study reflects the experience at a single transplant center, and may not be applicable to patients receiving non-myeloablative or autologous transplants. Fourth, there were a variety of reasons that prophylactic antibiotics were stopped or changed, including persistent fever and drug toxicity, and this study did not focus on the reasons for antibiotic failure or the incidence of toxicity. Fifth, the difference in antibiotic costs was very conservative and based only on drug acquisition costs. Since levofloxacin is administered once daily (oral or intravenous), whereas ceftazidime is administered 3 times a day intravenously, the total administration costs of ceftazidime are likely to be substantially higher than levofloxacin. We did

not calculate the administration costs of these medications because different institutions charge very different rates making the comparison less useful.

In conclusion, levofloxacin is an attractive antibiotic for prophylaxis in patients undergoing myeloablative allogeneic HCT and compared favorably to ceftazidime. The use of levofloxacin was associated with lower antibiotic acquisition costs and a reduction in significant bloodstream infections compared to ceftazidime. Levofloxacin resistant bacteria were detected in patients receiving levofloxacin prophylaxis but there was no significant increase in antibiotic resistant bacteria. Although patients receiving levofloxacin prophylaxis had a higher rate of developing fever, these patients were usually switched to ceftazidime, thereby helping to preserve extended spectrum antibiotics such as imipenem for those who fail empirical therapy. This strategy may help to further limit costs and the emergence of antibiotic resistance.

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Conflict of interest

The authors declare no conflict of interest.

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Table 1. Characteristics by prophylaxis regimen

	Ceftazidime	Levofloxacin
Number of patients	216	219
Sex (number, percent male)	107 (50)	132 (60)
Age (median, range in years)	42 (19 – 66)	43 (19 – 67)
Diagnosis (number, percent)		
Aplastic anemia	6 (3)	2 (1)
Acute lymphoblastic leukemia	24 (11)	26 (12)
Acute myeloid leukemia	65 (30)	77 (35)
Chronic myeloid leukemia	50 (23)	46 (21)
Myelodysplastic syndrome	52 (24)	55 (25)
Non-Hodgkin's lymphoma	12 (6)	9 (4)
Other	7 (4)	4 (2)
Disease risk (number, percent)		
Nonadvanced	152 (70)	145 (66)
Advanced	61 (28)	67 (31)
Missing	3 (1)	7 (3)
Conditioning regimen (number, percent)		
Bu/Cy	94 (44)	112 (51)
Bu/Cy/ATG	2 (1)	19 (9)
Bu/Flu	14 (6)	8 (4)
Cy/TBI	99 (46)	70 (32)
Other	7 (3)	10 (5)
Donor match (number, percent)		
Related	108 (50)	98 (45)
Unrelated	108 (50)	121 (55)
Cell source (number, percent)		
Bone marrow	61 (28)	42 (19)
Peripheral blood stem cell	150 (69)	177 (81)
BM, PBSC	3 (1)	0
Cord blood	2 (1)	0

Abbreviations: Bu=Busulfan, Cy=Cytoxan, ATG= Anti-thymocyte globulin, Flu= Fludarabine, TBI=total body irradiation

Table 2. Changes in antibiotic therapy after stopping initial regimen

	Ceftazidime	Levofloxacin
Number of patients	216	219
% of patients with antibiotic changes	45%	63%
Number of antibiotic changes	98	139
New therapy (per number of changes)		
Aztreonam	3 (3)	4 (3)
Ceftazidime	5 (5)	121 (87)
Ciprofloxacin	20 (20)	1 (1)
Clindamycin	1 (1)	4 (3)
Gentamicin	9 (9)	14 (10)
Imipenem	71 (72)	39 (28)
Levofloxacin	17 (17)	6 (4)
Vancomycin	25 (26)	37 (27)

Table 3. Etiology of bacteremic episodes diagnosed during first 100 days post-transplant by prophylaxis regimen

Category	Ceftazidime (196 infections)	Levofloxacin (159 infections)
Gram negative bacteremias		
Pseudomonas	3	3
Acinetobacter	0	5
Serratia	2	5
Stenotrophomonas	1	1
Total	14*	19*
Gram positive bacteremias		
Coagulase negative staphylococci	122*	107*
Staphylococcus aureus	2	1
Viridans streptococci	10	8
Enterococci	23	12
Bacillus spp	8	2
Corynebacteria	16	6
Listeria	0	1
Total	179*	137*
Anaerobic bacteremias	4	4
Mycobacterial bacteremias (M. avium)	1	0
Polymicrobial bacteremias	16	11

Recovery of any bacterium was recorded, including single isolates of CoNS or Corynebacteria

* Includes polymicrobial bacteremias

Table 4. Incidence of antibiotic resistance by prophylaxis regimen

				Resistance	
	Patient	**Episode**	**Day**	**Ceftazidime**	**Levofloxacin**
Pseudomonas					
Ceftazidime cohort	1	1	39	Intermediate	Resistant
	1	2	56	Sensitive	Resistant
	2	1	93	Sensitive	Sensitive
Levofloxacin cohort	3	1	54	Sensitive	Sensitive
	4	1	14	Sensitive	Resistant
	5	1	48	Sensitive	Sensitive
Acinetobacter					
Levofloxacin cohort	1	1	53	Sensitive	Sensitive
	2	1	42	Resistant	Resistant
	2	2	57	Resistant	Resistant
	2	3	86	Resistant	Resistant
	3	1	65	Sensitive	Sensitive
Serratia					
Ceftazidime cohort	1	1	29	Sensitive	Sensitive
	1	2	47	Sensitive	Sensitive
Levofloxacin cohort	2	1	55	Sensitive	Intermediate
	3	1	31	Sensitive	Sensitive
	3	2	42	Sensitive	Sensitive
	4	1	91	Sensitive	Sensitive
	5	1	48	Sensitive	Sensitive

Titles and legends to figures

Figure 1. Time to fever by initial prophylaxis regimen. The p-value results from a proportional hazards regression model adjusted for cell source and donor type.

Figure 2. Time to first bacteremia, excluding single-organism coagulase-negative Staphylococcus (CoNS) infection, by initial prophylaxis regimen. The p-value results from an unadjusted proportional hazards regression model.

Figure 3. Time to the first of any infection in blood (excluding CoNS), urine, respiratory or wound culture by initial prophylaxis regimen. The p-value results from a proportional hazards regression model adjusted for sex.

Figure 4. Relapse-free survival by initial prophylaxis regimen. The p-value results from a proportional hazards regression model adjusted for cell source and TBI exposure.