Incidence rate of fluoroquinolone resistant gram-negative rod bacteremia among allogeneic hematopoietic cell transplant patients during an era of levofloxacin prophylaxis

Arianna Miles-Jay

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2014

Committee:

Ali Rowhani-Rahbar

Steven Pergam

Program Authorized to Offer Degree:

Public Health, Epidemiology

University of Washington

Abstract

Incidence rate of fluoroquinolone resistant gram-negative rod bacteremia among allogeneic hematopoietic cell transplant patients during an era of levofloxacin prophylaxis

Arianna Miles-Jay

Chair of the Supervisory Committee:
Assistant Professor Ali Rowhani-Rahbar, MD, MPH, PhD
Department of Epidemiology

Background: There are concerns that emerging resistance to fluoroquinolones (FQ) may be leading to increasing rates of gram-negative rod (GNR) bacteremia in hematopoietic cell transplant (HCT) recipients. We set out to describe time trends in the incidence rates (IR) of GNR bacteremia and FQ-resistant GNR bacteremia in HCT recipients during an era of levofloxacin prophylaxis. **Methods:** We conducted a retrospective cohort study of adults undergoing allogeneic HCT between 2003 and 2012 at the Seattle Cancer Care Alliance (SCCA). Annual trends in the IRs of GNR bacteremia and FQ-resistant GNR bacteremia through 100 days post-transplant were assessed using Poisson regression. Cox proportional hazards regression was used to compare 30-day mortality between patients with FQ-resistant and those with FQ-sensitive GNR bacteremia. **Results:** Of the 2306 patients included in this cohort, 283 (12.3%) had GNR bacteremia. The IRs of GNR bacteremia and FQ-resistant GNR bacteremia increased from 2003 to 2009 and decreased afterwards; however, the overall annual trends were not significant (Incidence rate ratio [IRR] =1.01; 95% confidence interval [CI]: 0.98, 1.05 and IRR=1.03; 95% CI: 0.97, 1.10, respectively). FQ-resistant GNR bacteremia was associated with increased mortality compared to FQ-sensitive GNR bacteremia, even after adjustment for underlying disease severity, conditioning regimen, and age at transplant (Hazard ratio=2.31; 95% CI: 1.16, 4.62). **Conclusions:** On average, rates of FQ-resistant GNR bacteremia have not significantly changed at the SCCA over 10 years of FQ prophylaxis, although FQ-resistant GNR bacteremia is associated with increased mortality compared to FQ-sensitive GNR bacteremia.

INTRODUCTION

Bacterial bloodborne infections are a common cause of morbidity and mortality among allogeneic hematopoietic cell transplant (HCT) patients, occurring in up to 55% of this population.[1] Gram-negative rod (GNR) bacteremia affects between 5% and 11% of patients, and is associated with higher case-fatality than bacteremia caused by gram-positive organisms.[2–4] The majority of cancer/transplant centers worldwide utilize antibiotic prophylaxis during neutropenia to prevent GNR bacteremia and associated mortality in these highly immunocompromised patients.

International guidelines currently recommend the use of broad spectrum fluoroquinolones (FQ) for neutropenia prophylaxis in cancer and HCT recipients whose absolute neutrophil count is anticipated to decrease to ≤ 500/μL for at least seven days,[5–7] as they have been shown to reduce the incidence of GNR bacteremia in neutropenic patients and to decrease mortality in multiple randomized placebo-controlled trials.[8–10] Levofloxacin is the most frequently used agent due to its excellent bioavailability, oral formulation, and the convenience of once daily dosing.[11] While FQ prophylaxis has given more flexibility to outpatient cancer care, the most recent guidelines also warn that resistance should be closely monitored due to increasing FQ resistance worldwide. Recent studies of HCT recipients have suggested that the incidence of GNR bacteremia is increasing in this population,[1,12] including one study at our center.[13] Some have speculated that increasing FQ use and development of associated antimicrobial resistance may play a major role in this change.[12] However, available data that have examined the emergence of FQ-resistant GNR bacteremia among high-risk patient populations who receive FQ prophylaxis have been inconsistent.[1,12,14] Additionally, it is unknown if HCT recipients who develop FQ-resistant GNR bacteremia have an associated increased mortality when compared to patients who develop FQ-sensitive GNR bacteremia, as most studies have had insufficient power to address this important question.

Levofloxacin prophylaxis became standard practice for neutropenic prophylaxis for adult HCT recipients at the Seattle Cancer Care Alliance (SCCA)/Fred Hutchinson Cancer Research Center (FHCRC) in August 2002. In order to better understand trends in GNR bacteremia and FQ-resistant GNR bacteremia during this era of levofloxacin prophylaxis, we conducted a retrospective cohort study of

allogeneic HCT recipients who were transplanted between January 2003 and December 2012. Our primary goal was to determine annual trends in the incidence of GNR bacteremia and FQ-resistant GNR bacteremia during the first 100 days post-transplant in this cohort. In addition, we compared 30-day mortality between HCT recipients with FQ-resistant GNR bacteremia and those with FQ-sensitive GNR bacteremia.

METHODS

Study Population

All adults (≥18 years) who underwent an allogeneic HCT between 1/1/2003 and 12/31/2012 at the SCCA/FHCRC were eligible for inclusion in this study. For those patients who had multiple allogeneic transplants during the study period of interest, each transplant was considered separately. The study was approved by the FHCRC Institutional Review Board, and all participants provided written informed consent according to the principles of the Declaration of Helsinki.

Microbiologic assessment and antibacterial prophylaxis

Center based standard practice guidelines recommend that two sets of anaerobic and aerobic blood cultures are drawn when a patient presents with a fever, and daily blood cultures are recommended until an alternative source of the fever is identified or the patient defervesces. Although standard recommendations exist, blood cultures are ultimately drawn at the discretion of the healthcare teams. Similarly, the frequency of repeat blood cultures during this time period was determined by the primary healthcare provider, with the exception of surveillance blood cultures that are routinely drawn per protocol from patients who are treated with high dose glucocorticoids ($\geq$ 0.5mg/kg). Since steroids are known to blunt febrile responses,[15] these surveillance cultures are drawn bi-weekly while inpatient, weekly on outpatient discharge, and are discontinued following tapering of glucocorticoids to <0.5mg/kg. The vast majority of blood cultures in SCCA patients are drawn through central venous catheters or ports during post-HCT care; peripheral blood cultures are drawn at physician discretion.

HCT recipients at the SCCA/FHCRC receive 750 mg levofloxacin daily for prophylaxis at the start of neutropenia and continue until neutrophil recovery (ANC >500/μL); levofloxacin is re-started for patients whose ANC drops below 500/μL at other points during their post-transplant care. As per center-based standard practice guidelines, ceftazidime is the recommended empiric first-line antibiotic for neutropenic fever; routine use of vancomycin is only recommended if febrile patients also have high-grade mucositis. Ultimately, decisions regarding choice of antibiotics are at the discretion of the admitting healthcare team. All patients routinely receive additional antimicrobial prophylaxis with trimethoprim-sulfamethoxazole (TMP), dapsone, or atovaquone for *Pneumocystis jirovecii* (PJP) prophylaxis following ANC recovery. Patients also receive standard antifungal prophylaxis in the form of fluconazole or an extended spectrum azole (voriconazole or posconazole) as well as acyclovir or valacyclovir for herpes simplex/varicella zoster virus prophylaxis. All patients undergo CMV preemptive surveillance/therapy as has been previously described.[13]

Data collection

These data were extracted from prospectively collected databases maintained by the FHCRC that include demographic, laboratory, and clinical data from all patients undergoing HCT. Additional microbiologic data were collected through electronic medical record review. Allogeneic HCT recipients remain at the center for a minimum of 100 days post-transplant, assuring complete post-transplant data capture during this time period.

Definitions

GNR bacteremia was defined as the isolation of any GNR from a blood culture specimen. To reduce the likelihood of misclassifying repeat blood cultures from a primary bacteremia event as separate bacteremia events, positive cultures for the same organism collected ≤14 days from a prior positive culture were considered part of the primary event. Similarly, early post-transplant GNR events were excluded if the same organism was isolated in a pre-transplant culture in a similar 14-day window. Positive cultures for different bacterial genus/species, even if they occurred within 14 days from a documented GNR event,

were considered unique events. Cultures that isolated multiple GNR organisms on the same day were considered one GNR event and classified as polymicrobial bacteremia.

FQ-resistant GNR bacteremia was defined as the isolation of a GNR organism that was classified as either intermediate or resistant to levofloxacin or ciprofloxacin. Sensitivities to levofloxacin and ciprofloxacin were used because 1) they had routine sensitivities performed against them in our population and 2) FQ resistance is known to exhibit a "class effect", where a decrease in susceptibility to one drug likely means a similar decrease in all FQs.[16] FQ sensitivities were determined by the University of Washington Medical Center Microbiology Laboratory using Kirby-Bauer or E-tests, and interpreted using current Clinical and Laboratory Standards Institute (CLSI) guidelines at the time of GNR isolation.[17] Bacterial species that did not have current CLSI breakpoints for FQs at the time of specimen collection were excluded from resistance analyses. When evaluating FQ resistance, events were included if a previously isolated organism became resistant on follow-up blood cultures even if those were within 14 days of the initial culture. Similarly, polymicrobial bacteremia events were classified as FQ-resistant event if any of the isolated GNRs were determined to be intermediate or resistant to FQs.

Statistical analysis

For the primary evaluation of GNR incidence, we considered only the first GNR bacteremia event per transplant. The incidence rates of GNR bacteremia and FQ-resistant GNR bacteremia during 30 and 100 days post-transplant were calculated for each calendar year interval. Each patient contributed patient-days at risk from the day of transplant until death, re-transplant, 30 or 100 days post-transplant, or first GNR bacteremia event, whichever occurred first. Changes in incidence rates over time were assessed using a Poisson regression model, with time in one-year intervals as the main independent variable, and count of occurrence of a GNR bacteremia event post-transplant as the dependent variable. Patient-days at risk were included as an offset term to account for the varying follow-up time among transplants. Incidence rate ratios (IRR) were used as the measure of change. Clustered robust standard errors were used to account for the correlation between transplants of patients who underwent multiple transplants during our time period of interest.

Next, we conducted analyses considering all GNR bacteremia events for each transplant. In these analyses, each patient contributed patient-days at risk from the day of transplant until death, 30 or 100 days post-transplant, or re-transplant, whichever occurred first. The dependent variable in this analysis was the total count of GNR bacteremia events post-transplant. Changes in incidence rates over time were assessed using similar methods to those described above.

For all analyses, estimated changes in incidence rates were first calculated in unadjusted models to assess the average overall change regardless of the mechanism. We then constructed models that included known risk factors for GNR bacteremia. These covariates were selected *a priori* and included: age at transplant, severity of underlying illness (low, medium, and high), conditioning regimen score (nonmyeloablative, non-total-body irradiation, total-body irradiation with ≤12 Gray (Gy), total-body irradiation with >12 Gy), presence of severe gut graft versus host disease (GVHD, ≥grade 2), and graft type (bone marrow, peripheral blood, or cord blood). Severity of underlying illnesses categories were defined by outcomes previously observed at our center, while conditioning regimens were first divided into nonmyeloablative and myeloablative, with myeloablative further subdivided by dose of total-body-irradiation used.[18] Following the examination of the main results, we elected to conduct post-hoc exploratory analyses to quantify the trends of GNR bacteremia and FQ-resistant GNR bacteremia incidence rates between 2003 and 2009 and separately for 2009 to 2012. These analyses were conducted for first events, all events, day 0-30, and day 0-100. Changes in incidence rates over time were assessed using the same methods described above.

Lastly, the 30-day all-cause cumulative mortality was compared between patients who developed FQ-resistant GNR bacteremia and those who developed FQ-sensitive GNR bacteremia using Kaplan Meier estimates and the log-rank test. Cox proportional hazards regression models were used to compare the risk of death during 30-days following the first positive GNR blood culture. These analyses were performed both without adjustment for any covariates and with adjustment for underlying disease severity, conditioning regimen score (both defined above), and age at transplant. All analyses were performed using Stata version 13 (StataCorp, College Station, TX).

RESULTS

Of the 2306 transplants included in this cohort, 283 (12.3%) experienced at least one GNR bacteremia event during the first 100 days post-transplant. In the first event analysis of patients with available resistance data (n=256), there were 84/256 (33%) FQ-resistant events, and 172/256 (67%) FQ-sensitive events; 27 GNR events had no resistance data available. The selected demographic and clinical characteristics of patients who experienced a GNR bacteremia event and those that did not were very similar, with the exception that patients who experienced GNR bacteremia were more likely to have severe gut GVHD (Table 1).

Time trends in incidence rate of all GNR bacteremia

When including only the first GNR bacteremia event per transplant, the overall incidence rate of GNR bacteremia was 1.38 events per 1000 patient-days (PD) (95% CI 1.22, 1.55). The incidence rates varied over time, starting at 0.91 events per 1000 PD in 2003 (95%CI 0.56, 1.41), peaking at 2.33 events per 1000 PD in 2009 (95% CI 1.71, 3.11), and declining to its lowest in 2012 at 0.63 events per 1000 PD (95% CI 0.34, 1.08) (Figure 1a). On average, the incidence rate of GNR bacteremia increased annually between 2003 and 2012 by 1%, although this trend was not significant (IRR=1.01, 95%CI: 0.98, 1.05) (Table 2).

A post-hoc analysis revealed an average annual increase of the incidence rate of GNR bacteremia of 16% (IRR= 1.16, 95%CI: 1.08, 1.24) between 2003 and 2009 and an average annual decrease of 33% (IRR=0.67, 95%CI 0.56, 0.80) between 2009 and 2012. When only considering events that occurred between days 0 and 30 post-transplant, all trends over time were in the same direction as described above, but none were statistically significant (Table 2). Adjusting for known risk factors for bacteremia did not meaningfully change the associations observed in unadjusted analyses (Table 2). Results from the multiple events analyses demonstrated similar results, with minimal increases in the incidence rates of GNR bacteremia compared to the first event analysis (Table 2 and Figure 1b).

Time trends in incidence rate of FQ-resistant GNR bacteremia

The incidence rate of FQ-resistant GNR bacteremia generally displayed similar patterns as the incidence rate of all GNR bacteremia. In the first event analysis, the overall incidence rate of FQ-resistant GNR bacteremia was 0.41 events per 1000 PD (95% CI 0.33, 0.51). The incidence rates varied over time, starting at 0.14 events per 1000 PD in 2003, peaking at 0.81 events per 1000 PD in 2009, and decreasing to 0.19 events per 1000 PD in 2012 (Figure 1a). On average, the incidence rate of FQ-resistant GNR bacteremia increased annually between 2003 and 2012 by 3%, although this trend was not significant (IRR=1.03, 95%CI: 0.97, 1.10) (Table 2).

A post-hoc analysis revealed an average annual increase of the incidence rate of FQ-resistant GNR bacteremia of 23% (IRR= 1.23, 95%CI: 1.08, 1.40) between 2003 and 2009 and an average annual decrease of 38% (IRR=0.62, 95% CI 0.45, 0.86) between 2009 and 2012. When only considering events that occurred between days 0 and 30 post-transplant, all trends over time were in the same direction as described above, but none were statistically significant (Table 2). Adjusting for known risk factors for bacteremia did not meaningfully change the associations observed in unadjusted analyses (Table 2). Results from the multiple events analysis again found similar results, including minimal overall increases in the incidence rates of FQ-resistant GNR bacteremia compared to the first event analysis.

Survival analysis by FQ resistance

Patients who had an initial FQ-resistant GNR bacteremia event had a significantly higher 30-day post-event cumulative mortality than patients who experienced a FQ-sensitive event (20.7% vs. 9.4%, p=0.0089) (Figure 2). In an unadjusted survival analysis, patients with FQ-resistant GNR bacteremia had an increased risk of death through 30-days post GNR isolation than patients with FQ-sensitive bacteremia (HR 2.43, 95% CI: 1.23, 4.80). This association persisted after adjustment for severity of underlying illness, conditioning regimen score, and age at transplant (HR 2.31, 95% CI: 1.16, 4.62).

DISCUSSION

In this large single center retrospective cohort study, we examined trends in the incidence of GNR bacteremia and FQ-resistant GNR bacteremia among adult allogeneic HCT recipients over a decade during which levofloxacin was used for neutropenic prophylaxis. We found that, on average, there was no significant trend in the incidence rates of GNR bacteremia and FQ-resistant GNR bacteremia between 2003 and 2012 in this population. In post-hoc analyses, we found that the incidence rates of GNR bacteremia and FQ-resistant GNR bacteremia increased annually between 2003 and 2009, and then decreased between 2009 and 2012, although that decrease was not significant for FQ-resistant GNR bacteremia. Importantly, these data also demonstrate that patients who developed bacteremia from FQ-resistant GNRs had higher 30-day mortality than those who developed bacteremia from FQ-sensitive GNRs.

Other centers have described rising rates of GNR infections in HCT patients, but few studies have either studied trends in GNR bacteremia over time, or assessed such data after a major change in neutropenic antibiotic prophylaxis. The findings of studies that sought to quantify this association have been inconsistent, with at least one center reporting significantly increasing rates of GNR bacteremia during use of levofloxacin prophylaxis,[1] and another reporting no significant change.[12] Available data on the issue of FQ-resistance in patient populations receiving FQ prophylaxis also varies between centers. Some have described non-significant increases in the proportion of GNR isolates that are FQ-resistant during the modern era of FQ prophylaxis, [3,19] while others, including a previous study at our center, reported no evidence of changes in rates of FQ-resistant GNR bacteremia after initiation of levofloxacin prophylaxis.[11,14] In contrast, other centers have described significantly increasing rates of FQ-resistant GNR during FQ prophylaxis,[12,20] including one that only measured FQ-resistant *Escherichia coli.*[20] Our data are most consistent with studies that identified no significant overall increase in GNR bacteremia or FQ-resistant GNR bacteremia over time. To our knowledge, none of these studies have addressed survival differences between HCT patients who developed FQ-resistant GNR bacteremia and those who developed FQ-sensitive bacteremia, however, FQ resistance has been identified as an independent risk factor for death after infection in other populations.[21]

The observed patterns of incidence rates in this study were somewhat unexpected. The most recent data from our center indicated that rates of GNR bacteremia had been increasing.[13] We hypothesized that this increase might be associated with our widespread use of levofloxacin prophylaxis, especially if the increasing rates of GNR bacteremia were accompanied by increasing rates of FQ-resistant GNRs. Our post-hoc analyses confirmed this increase through 2009, but rates of GNR bacteremia steeply decreased between 2009 and 2012. There are likely several contributing factors to the unforeseen decrease in GNR bacteremia events after 2009 in this population. Several infection control interventions were implemented between 2009 and 2010, including the initiation of chlorhexidine gluconate (CHG) baths in January 2010, the development and implementation of a new line bundle also in January 2010, adoption of "scrub the hub" [22] as a standardized protocol in September 2010, and a switch to CHG impregnated dressings in February 2009. Since such interventions have been associated with decreased rates of bloodborne infections,[23–25] it is possible that together, these interventions contributed to the decrease in GNR bacteremia between 2009 and 2012.

It is also important to note that standard practice changed in 2010 to discontinue collection of an extra set of blood cultures that were held for yeast and fungi. With improvements in microbiologic techniques, such methods provided no additional benefit in isolating fungal pathogens in these patients. It is possible that these extra cultures cultivated bacterial growth, and their discontinuation could have contributed to the decrease in isolation of GNR organisms. Additionally, UW Microbiology changed their blood culture system in 2010, potentially resulting in differential isolation of organisms. To address these issues, we examined the number of blood cultures ordered between 2003 and 2012, and these data demonstrated a similar time trend as the incidence rates of GNR bacteremia, suggesting that these laboratory changes did not contribute significantly to our results (data not shown). We hypothesize that many of the aforementioned factors influenced the observed recent decline in rates of GNR bacteremia, however, this study was not designed to directly attribute changes in incidence to any of these infection control interventions or laboratory variations.

Perhaps most importantly, we did not observe an increase in FQ-resistant GNR bacteremia with widespread use of levofloxacin as neutropenic prophylaxis in this population. One reason for this might be shorter periods of neutropenia and subsequent exposure intervals to levofloxacin in this population driven

by a gradual increase in the number of nonmyeloablative transplants at our center over time. Another explanation is that although there is no significant change in resistance patterns overall, there could be changing resistance patterns in specific species of GNR organisms, as some have shown that the impact of FQ use on resistance may vary by organism.[26] FQs are unique in that they are synthetic antibiotics, and it was thought that they might therefore be more insulated from resistance issues. Unfortunately, overuse in medicine and in agriculture has led to reports of increasing rates of FQ resistance worldwide.[27] Lack of a significant increase in FQ-resistance observed in this study suggests that levofloxacin may continue to be a viable neutropenic prophylaxis agent in this population.

Lastly, these data show that patients with FQ-resistant GNR bacteremia had an almost 2.5 fold increased risk of death within 30-days post-infection compared to patients with FQ-sensitive GNR bacteremia. This association persisted even after adjusting for underlying disease severity, type of conditioning regimen, and age at transplant, suggesting that FQ resistance may be an independent risk factor for death in patients with GNR bacteremia. One mechanism that may explain such differences is that patients with resistant infections experience a delay in receiving adequate antimicrobial therapy, resulting in poorer outcomes.[28] Further research is needed to elucidate risk factors for the development of resistant infections, to allow for prompt identification and treatment of these patients. Overall, these data highlight the serious nature of antimicrobial resistance and the importance of continued vigilance and monitoring of FQ resistance trends in HCT recipients and other high-risk populations.

The retrospective and observational nature of this study imposes limits on the interpretation of our data. There are likely variables that have changed over time and that influence GNR bacteremia rates or FQ resistance for which we could not adjust. Additionally, there were organisms that lacked FQ sensitivity data and could not be included in the FQ resistance analysis, and it is possible that changes in the incidence of these unclassifiable organisms over time may have had a minimal effect on our results. Finally, these data only reflect the experience of a single transplant center and may not be generalizable to other institutions. Regional variances in transplant conditioning, antimicrobial therapy, and prevalence of FQ-resistance could impact GNR bacteremia trends at other centers. However, strengths of this study include the large sample size and the valuable long-term longitudinal data, which inform evidence based decisions about use of FQ prophylaxis at our center.

In summary, these data demonstrate that rates of FQ-resistant GNR bacteremia have not significantly increased during an era of levofloxacin prophylaxis in adult allogeneic HCT recipients at our large comprehensive cancer. Recent decreases in incidence rates of GNR bacteremia were potentially a result of a combination of center-wide changes, including several important infection control interventions. Although there is no evidence that levofloxacin prophylaxis is associated with an increase in FQ-resistant infections in HCT recipients at our center, the increased mortality associated with FQ-resistant GNR bacteremia re-enforces the importance of monitoring emerging FQ resistance in this high-risk population.

Table 1: Selected characteristics of adult allogeneic HCT transplants by occurrence of GNR bacteremia within 100 days post-transplant

Variable	GNR event n=283 n (%)	No GNR events n=2023 n (%)
Age (years)—median (IQR)	53 (18)	51 (20)
Sex		
Male	149 (52.7)	1214 (60.0)
Female	134 (47.3)	809 (40.0)
Race		
Caucasian	218 (80.4)	1651 (85.0)
Black	10 (3.7)	28 (1.4)
Hispanic	16 (5.9)	59 (3.0)
Asian/Pacific Islander	13 (4.8)	100 (5.2)
Native American	2 (0.7)	18 (0.9)
Other	12 (4.4)	87 (4.5)
Stem-cell source		
Bone marrow	44 (15.6)	273 (13.5)
Bone marrow and PBSC	2 (0.7)	2.9 (0.10)
PBSC	216 (76.3)	1640 (81.7)
Cord blood	21 (7.4)	108 (5.3)
Diagnosis		
Acute leukemia	130 (45.9)	935 (46.2)
Multiple myeloma	16 (5.7)	114 (5.6)
Myelodysplastic syndrome	43 (15.2)	402 (19.9)
Non-Hodgkin lymphoma	36 (12.7)	210 (10.4)
Other	58 (20.5)	362 (17.9)
Underlying Disease Severity		
Low	41 (14.5)	284 (14.0)
Medium	143 (50.5)	1013 (50.1)
High	99 (35.0)	726 (35.9)
Conditioning regimen score		
Nonmyeloablative	126 (44.5)	826 (40.8)
Non-total-body irradiation	79 (27.9)	662 (32.7)
Total-body irradiation with ≤12 Gy	67 (23.7)	471 (23.3)
Total-body irradiation with >12 Gy	11 (3.9)	64 (3.2)
Severe Gut GVHD (≥ grade 2)*		
Yes	221 (78.1)	1843 (91.4)
No	62 (21.9)	174 (8.6)

*Number does add to n due to missing data

Table 2: Unadjusted and adjusted time trends in incidence rates of GNR bacteremia, 2003-2012

		Overall			FQ-resistant		
		2003-2012	2003-2009	2009-2012	2003-2012	2003-2009	2009-2012
		Unadjusted			Unadjusted		
		IRR (95% CI)[a]			IRR (95% CI)[a]		
First Event	Overall (0-100)	1.01 (0.98, 1.05)	1.16 (1.08, 1.24)	0.67 (0.56, 0.80)	1.03 (0.97, 1.10)	1.23 (1.08, 1.40)	0.62 (0.45, 0.86)
	Month 1 (0-30)	1.02 (0.94, 1.09)	1.04 (0.91, 1.19)	0.82 (0.62, 1.10)	1.08 (0.96, 1.21)	1.12 (0.89, 1.40)	0.87 (0.57, 1.33)
Multiple Events	Overall (0-100)	1.02 (0.98, 1.06)	1.17 (1.10, 1.26)	0.68 (0.57, 0.81)	1.01 (0.95, 1.08)	1.18 (1.03, 1.36)	0.61 (0.44, 0.84)
	Month 1 (0-30)	1.03 (0.96, 1.10)	1.07 (0.94, 1.21)	0.86 (0.64, 1.14)	1.07 (0.96, 1.21)	1.12 (0.89, 1.40)	0.87 (0.56, 1.32)
		Adjusted			Adjusted		
		aIRR (95% CI)[a,b]			aIRR (95% CI)[a,b]		
First Event	Overall (0-100)	1.00 (0.97, 1.04)	1.14 (1.06, 1.22)	0.67 (0.55, 0.80)	1.02 (0.95, 1.09)	1.19 (1.04, 1.36)	0.62 (0.45, 0.87)
	Month 1 (0-30)	0.99 (0.91, 1.07)	0.97 (0.84, 1.11)	0.86 (0.63, 1.18)	1.04 (0.91, 1.18)	1.00 (0.78, 1.28)	0.88 (0.55, 1.40)
Multiple Events	Overall (0-100)	1.01 (0.98, 1.05)	1.16 (1.08, 1.24)	0.67 (0.56, 0.81)	0.99 (0.92, 1.07)	1.13 (0.99, 1.30)	0.61 (0.44, 0.84)
	Month 1 (0-30)	1.01 (0.93, 1.09)	1.00 (0.87, 1.14)	0.90 (0.65, 1.23)	1.04 (0.91, 1.18)	1.00 (0.78, 1.28)	0.88 (0.56, 1.38)

[a] IRR = incidence rate ratio, CI = confidence interval [b] Adjusted for underlying disease severity, conditioning regimen score, presence of severe gut GVHD, graft type, and age at transplant.

Figure 1a: Incidence rate of first GNR bacteremia event, by transplant year, 2003-2012

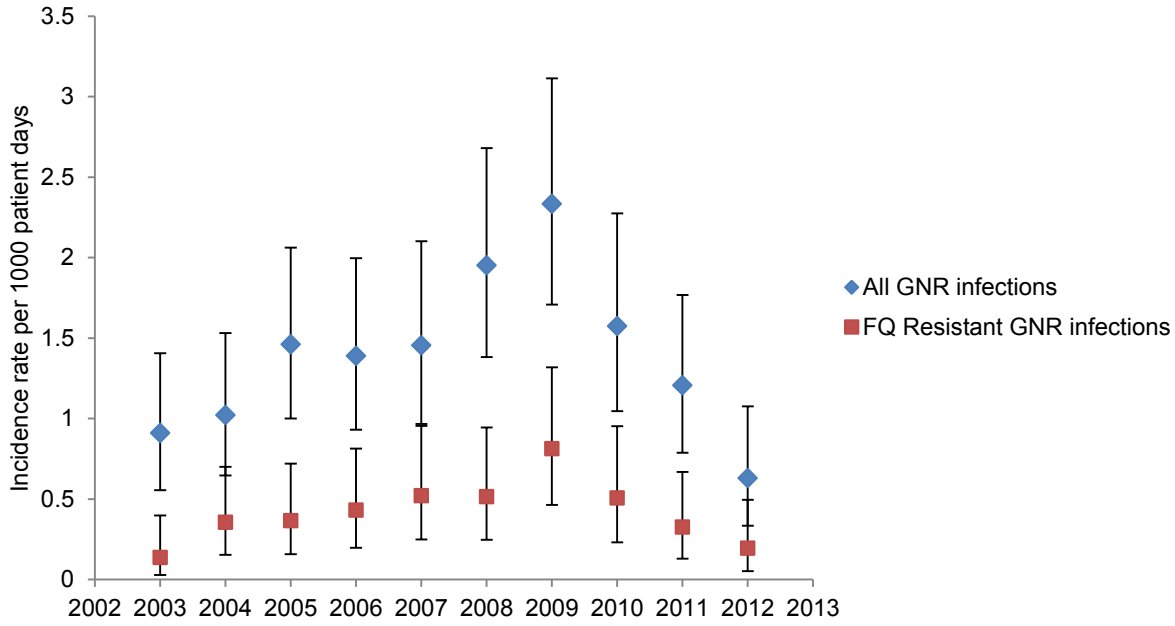


Figure 1b: Incidence rate of all GNR bacteremia events, by transplant year, 2003-2012

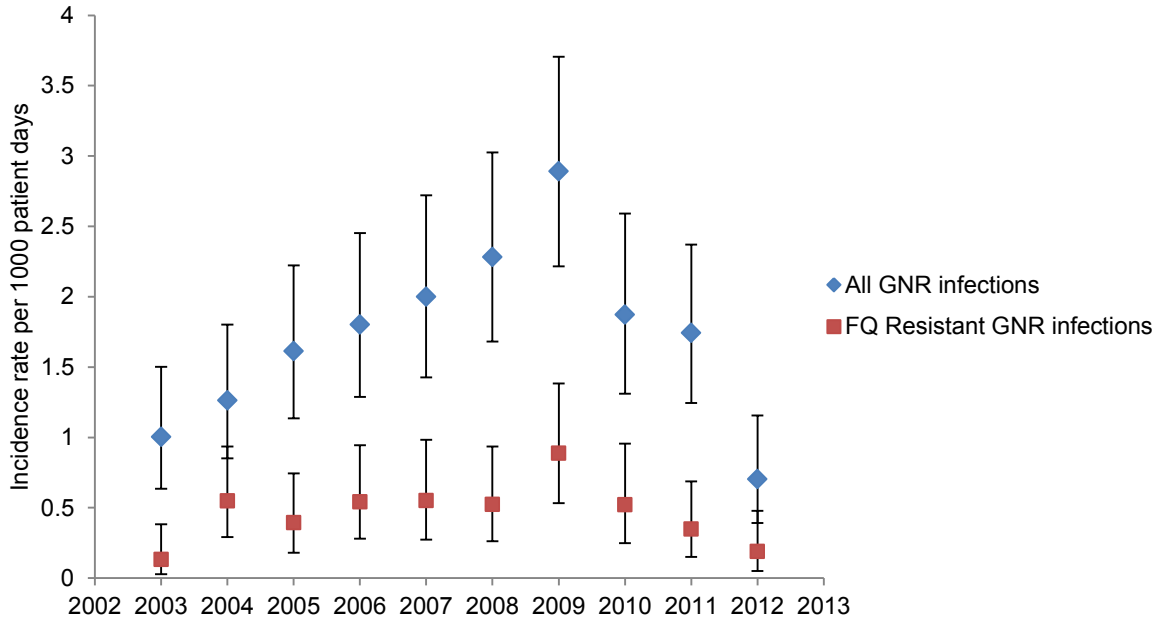
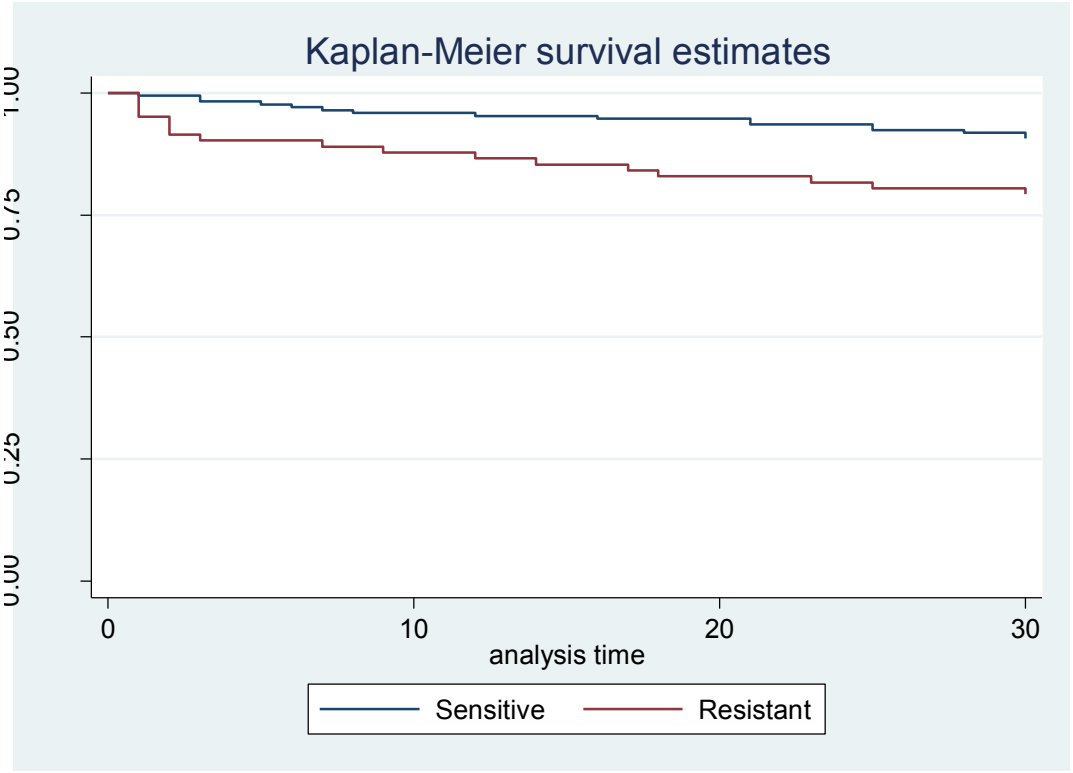


Figure 2: Kaplan-Meier survival estimates 30-days post first infection, by FQ resistance status



References

1. Mikulska M, Del Bono V, Raiola AM, et al. Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: reemergence of Gram-negative rods and increasing antibiotic resistance. *Biol Blood Marrow Transplant*. 2009;15(1):47–53.

2. Collin B a, Leather HL, Wingard JR, Ramphal R. Evolution, incidence, and susceptibility of bacterial bloodstream isolates from 519 bone marrow transplant patients. *Clin Infect Dis*. 2001;33(7):947–53.

3. Bock AM, Cao Q, Ferrieri P, Young J-AH, Weisdorf DJ. Bacteremia in blood or marrow transplantation patients: clinical risk factors for infection and emerging antibiotic resistance. *Biol Blood Marrow Transplant*. 2013;19(1):102–8.

4. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2010;363(22):2091–101.

5. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15(10):1143–238.

6. National Comprehensive Cancer Network. Prevention and treatment of cancer related infections. Version I.2013

7. Girmenia C, Menichetti F. Neutropenia and Infections Current Epidemiology and Prevention of Infectious Complications. *European Oncology & Haematology.* 2011;7(4):270-277.

8. Bucaneve G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med*. 2005;353(10):977–87.

9. Cullen M, Steven N, Billingham L, et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *N Engl J Med*. 2005;353(10):988–98.

10. Gafter-Gvili A, Fraser A, Paul M, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane database Syst Rev*. 2012;1(4):CD004386.

11. Guthrie K a, Yong M, Frieze D, Corey L, Fredricks DN. The impact of a change in antibacterial prophylaxis from ceftazidime to levofloxacin in allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2010;45(4):675–81.

12. Therriault BL, Wilson JW, Barreto JN, Estes LL. Characterization of bacterial infections in allogeneic hematopoietic stem cell transplant recipients who received prophylactic levofloxacin with either penicillin or doxycycline. *Mayo Clin Proc*. 2010;85(8):711–8.

13. Green ML, Leisenring W, Stachel D, et al. Efficacy of a viral load-based, risk-adapted, preemptive treatment strategy for prevention of cytomegalovirus disease after hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2012;18(11):1687–99.

14. Simondsen K a, Reed MP, Mably MS, Zhang Y, Longo WL. Retrospective analysis of fluoroquinolone prophylaxis in patients undergoing allogeneic hematopoietic stem cell transplantation. *J Oncol Pharm Pract*. 2013;19(4):291–7.

15. Tatro JB. Endogenous antipyretics. *Clin Infect Dis*. 2000;31 Suppl 5:S190–201.

16. Becnel Boyd L, Maynard MJ, Morgan-Linnell SK, et al. Relationships among ciprofloxacin, gatifloxacin, levofloxacin, and norfloxacin MICs for fluoroquinolone-resistant Escherichia coli clinical isolates. *Antimicrob Agents Chemother*. 2009;53(1):229–34.

17. Performance Standards for Antimicrobial Susceptibility Testing: Twenty-second International Supplement. CLSI document M100-S22: 2012.

18. Parimon T, Au DH, Martin PJ, Chien JW. A risk score for mortality after allogeneic hematopoietic cell transplantation. *Ann Intern Med*. 2006;144(6):407–14.

19. Mikulska M, Del Bono V, Raiola AM, et al. Enterococcal bloodstream infection after hematopoietic stem cell transplant: experience of a center with a low prevalence of vancomycin-resistant enterococci. *Clin Infect Dis*. 2012;55(12):1744.

20. Kern W V, Klose K, Jellen-Ritter a S, et al. Fluoroquinolone resistance of Escherichia coli at a cancer center: epidemiologic evolution and effects of discontinuing prophylactic fluoroquinolone use in neutropenic patients with leukemia. *Eur J Clin Microbiol Infect Dis*. 2005;24(2):111–8.

21. Lautenbach E, Metlay JP, Bilker WB, Edelstein PH, Fishman NO. Association between fluoroquinolone resistance and mortality in Escherichia coli and Klebsiella pneumoniae infections: the role of inadequate empirical antimicrobial therapy. *Clin Infect Dis*. 2005;41(7):923–9.

22. Simmons S, Bryson C, Porter S. “Scrub the hub”: cleaning duration and reduction in bacterial load on central venous catheters. *Crit Care Nurs Q*. 2011;34(1):31–5.

23. Bleasdale SC, Trick WE, Gonzalez IM, Lyles RD, Hayden MK, Weinstein R a. Effectiveness of chlorhexidine bathing to reduce catheter-associated bloodstream infections in medical intensive care unit patients. *Arch Intern Med*. 2007;167(19):2073–9.

24. Galpern D, Guerrero A, Tu A, Fahoum B, Wise L. Effectiveness of a central line bundle campaign on line-associated infections in the intensive care unit. *Surgery*. 2008;144(4):492–5; discussion 495.

25. Sannoh S, Clones B, Munoz J, Montecalvo M, Parvez B. A multimodal approach to central venous catheter hub care can decrease catheter-related bloodstream infection. *Am J Infect Control*. 2010;38(6):424–9.

26. Kern W V, Steib-Bauert M, de With K, et al. Fluoroquinolone consumption and resistance in haematology-oncology patients: ecological analysis in two university hospitals 1999-2002. *J Antimicrob Chemother*. 2005;55(1):57–60.

27. Robicsek A, Jacoby G a, Hooper DC. The worldwide emergence of plasmid-mediated quinolone resistance. *Lancet Infect Dis*. 2006;6(10):629–40.

28. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest*. 2000;118(1):146–55.