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MAJOR ARTICLE

The Prevalence of Multidrug Resistance in Enterobacterales Is Higher in Patients Undergoing Hematopoietic Stem Cell Transplantation

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Background. Antimicrobial resistance is a global public health emergency. Patients undergoing hematopoietic stem cell transplantation (HCT) are at increased risk for severe infections with multidrug-resistant (MDR) organisms, although more data are needed on the relative burden of MDR Enterobacterales (MDR-E) in immunocompromised populations. In this study, we compare the prevalence of Enterobacterales resistance in cultures from patients undergoing HCT with that of non-HCT patients seeking care at a large healthcare system in North Carolina, USA.

Methods. We analyzed electronic health data from 52 067 patients aged ≥18 years with a culture positive for Enterobacterales species (2000–2023). Of these, 271 had undergone HCT prior to culture-recovered Enterobacterales. We compared resistance trends over time for specific antibacterial classes using a 5-year moving average and used generalized linear models to estimate prevalence ratios and differences of MDR-E in HCT versus non-HCT patients.

Results. HCT recipients overall had a higher prevalence of MDR-E (37.7% vs 19.4%) and resistance for all individual antibiotic classes analyzed. Comparing HCT vs non-HCT groups, the highest prevalence ratio was observed for resistance to aminoglycosides (2.10 [95% confidence interval {CI}, 1.65–2.68]); the largest adjusted absolute difference in nonsusceptibility was observed with quinolones (20.4 [95% CI, 14.9–25.8]). MDR-E infections were associated with double all-cause mortality at 1 year.

Conclusions. This large longitudinal study highlights how antimicrobial resistance has consistently been a substantial problem in HCT recipients over the prior 2 decades. Targeting antimicrobial resistance mitigation efforts will be key in reducing the risk of MDR infections in HCT.

Keywords. antimicrobial resistance; blood and marrow transplantation; Enterobacterales infection; hematopoietic stem cell transplantation; multidrug-resistant organisms.

Rising rates of antimicrobial resistance (AMR) globally are a threat to public health everywhere and necessitate quantifying the burden of AMR, especially in high-risk populations [1, 2]. High-burden populations such as those undergoing hematopoietic stem cell transplantation (HCT) are few in number relative to the general population but may serve as a source for spread of AMR in both hospitals and the community. Patients undergoing HCT comprise a cohort at the highest risk for infection within any hospital system, receiving a disproportionate amount of antimicrobial prophylaxis and treatment that contributes to significant antimicrobial selection pressure. Enterobacterales in particular, is a clinically important order of gram-negative bacteria (GNB) that harbor a large number of AMR genes and are responsible for the majority of multidrug-resistant (MDR) infections among hospitalized patients [3–6]. Risk factors for MDR Enterobacterales (MDR-E) infection encompass the experience of HCT recipients, including extended hospital stays, extensive antibiotic exposure, and significant immunosuppression [7]. Infections with MDR organisms are even becoming more common outside of the hospital in community-dwelling populations [8].

While rates of MDR-E are known to be greater in HCT recipients compared to the general population, the additional burden of resistance in this population remains poorly characterized [9, 10]. More extensively documented is that MDR GNB colonization increases not only the risk for infection but is also associated with an

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increased risk of prolonged hospitalization and mortality [10–12]. For example, colonization with fluoroquinolone-resistant and extended-spectrum β-lactamase–resistant Enterobacterales has been demonstrated to increase the risk of bloodstream infection with those same colonizing and antibiotic-resistant strains [10–13]. Use of fluoroquinolones therefore increases the risk of infection with fluoroquinolone-resistant Enterobacterales, decreasing the effectiveness of this commonly used drug for antibacterial prophylaxis [14, 15]. Despite this concern, the overwhelming majority of transplant programs continue to use fluoroquinolones as prophylaxis.

More data on the additional burden of MDR-E infection in high-risk populations such as those undergoing HCT are needed to inform the allocation of resources for AMR prevention. In this study, we compare the prevalence of MDR and other AMR in Enterobacterales isolates in HCT patients relative to the population of non-HCT patients seeking care in a large healthcare system located in North Carolina (UNC).

METHODS

Patients

We compared the prevalence of AMR in Enterobacterales isolates from HCT recipients to that in isolates from the non-HCT population. We used UNC Health institutional electronic health record (EHR) data from patients in the UNC Health System from 1 March 2000 to 30 September 2023. The EHR includes patients seen at the UNC Medical Center. An earlier version of this cohort has been published previously [6].

We included patients in our study from the UNC Health system who had at least 1 clinical culture with growth of an Enterobacterales species and who were aged ≥18 years on the date the culture was obtained ("Enterobacterales database," Supplementary Figure 1). We included patients in the study cohort only if their cultures were obtained from UNC Health system locations at which HCT recipients had also been seen. HCT recipients with Enterobacterales cultures were identified from a manually curated database of 3284 patients who had undergone HCT at UNC Chapel Hill at any point through September 2022. We included only those cultures obtained after the HCT infusion date. We merged medical record numbers from HCT recipients with the Enterobacterales database to characterize patients in our study cohort as either HCT or non-HCT (Supplementary Figure 1). We then removed patients from the non-HCT group who had undergone an HCT at UNC at any time. All patients undergoing HCT at UNC receive standard antimicrobial prophylaxis including levofloxacin prior to engraftment (absolute neutrophil count >500 cells/μL) and trimethoprim-sulfamethoxazole for at least 6 months post-HCT.

We collected the following for each isolate: culture date, patient date of birth, specimen source (eg, blood, urine, respiratory), location of culture collection (eg, hospital department or clinic name), and patient ZIP code. We selected the first isolate of a given Enterobacterales species per patient, excluding repeat cultures of a species, and grouped all specimen sources as "blood," "urine," "respiratory," or "other." We grouped locations where cultures were obtained as "inpatient," "outpatient," "emergency," or "other."

Patient Consent Statement

The UNC Office of Human Research Ethics/Institutional Review Board approved the study protocol. Informed consent was not required for inclusion in this study as it did not include factors necessitating patient consent.

Microbiology

We obtained microbiological data from the UNC Hospitals Clinical Microbiology Laboratory, including species and antibiotic susceptibility data on bacterial isolates obtained during any hospitalization, clinic, or emergency department visit. Susceptibility breakpoints for some antibiotics changed during the study period; we therefore used numeric zone of inhibition measurements or minimum inhibitory concentrations (MICs) to standardize susceptibility interpretations to the most current Clinical and Laboratory Standards Institute (CLSI) breakpoints as appropriate.

We considered specific species nonsusceptible for antibiotics if the zone of inhibition or MIC interpretation was "intermediate" or "resistant" using current breakpoints. We determined nonsusceptibility for a class of antibiotics if it was nonsusceptible to at least 1 member of that class, after removing intrinsically resistant species-antibiotic combinations. We designated an isolate MDR based on nonsusceptibility to at least 1 antibiotic from at least 3 separate antibiotic classes [16]. We removed susceptibility results for first-generation cephalosporins due to separate breakpoints for cefazolin depending on the type of isolate (eg, complicated vs uncomplicated urinary tract infections). We classified "anti-*Pseudomonal* cephalosporins" as either the fourth-generation cefepime or third-generation ceftazidime as these are commonly used in initial empiric treatment of febrile neutropenia in patients undergoing HCT; ceftazidime was removed from the category of third-generation cephalosporins for this reason. Third-, fourth-, and fifth-generation cephalosporins were grouped together as "3+ cephalosporins." Other antibiotic class definitions are based on those published previously [6].

Statistical Analysis

Our primary outcome of interest was MDR-E, with secondary analysis including isolates with nonsusceptibility to clinically relevant antibiotic classes. Covariates extracted from the EHR were patient age at the time of culture, sex, race ("white," "black," "other"), specimen source ("blood," "urine," "respiratory,"

"other"), date of specimen collection, location of culture collection ("inpatient," "outpatient," "emergency," and "other"), and socioeconomic status (as described below). We analyzed the association between each covariate and prevalence of MDR-E. To assess the association of age with MDR-E prevalence, we used restricted cubic splines; based on the functional form of age and MDR-E prevalence, we dichotomized age as ≤50 or >50 years for the association analysis.

To obtain the variable socioeconomic status (SES), we used methodology previously described by the Centers for Disease Control and Prevention [17]. Home ZIP (postal) codes for all patients were obtained at the time of culture and transformed into an SES subscore of the Social Vulnerability Index as described previously [18]. The score represents the summed percentile ranking of a given ZIP code in 5 areas: poverty rate, unemployment rate, cost-burdened housing rate, the percentage of residents who lack health insurance, and the percentage of adult residents who lack a high-school diploma. Data on these variables were obtained from the 2020 five-year American Community Survey (data.census.gov). To allow for more facile interpretation of the association between multidrug resistance and SES, SES was divided into equal-sized quartiles: high (1), medium-high (2), medium-low (3), and low (4).

To explore trends over the study period, we calculated the 5-year moving average using the crude proportions of isolates that were nonsusceptible to each antibiotic class or that were MDR. Using generalized linear models, we estimated prevalence ratios and differences as measures of association, with 95% confidence intervals (CIs).

In multivariable models assessing both the association between HCT and MDR-E, and the risk of death from any cause at 90 days and 1 year, we modeled age and year as continuous variables using restricted cubic splines. Categorical variables were sex, race, specimen source, location, SES, and culture year. We used a Poisson distribution with a robust variance estimator to estimate prevalence ratios and a Gaussian distribution with a robust variance estimator to estimate prevalence differences. To compare time to death from any cause between HCT patients with MDR-E versus those with more susceptible strains, we plotted survival curves using the Kaplan-Meier estimator. Finally, as we determined that location type (inpatient, outpatient, intensive care unit, emergency) was significantly different between non-HCT and HCT groups, we performed sensitivity analyses using only culture data obtained inpatient (included in Supplementary Data). A 2-sided P value of <.05 was considered statistically significant. All analyses were performed using R software (version 4.2.1).

RESULTS

Study Participants and Enterobacterales Isolates

From March 2000 to September 2023, 59 777 Enterobacterales isolates from 52 338 unique patients were identified that met inclusion criteria. We merged the Enterobacterales database of the general UNC Health population with a manually curated database of 3284 patients who had undergone HCT at UNC (Supplementary Figure 1).

Overall, HCT recipients were of comparable age and ethnicity with the general population but were more likely to be male than those of the non-HCT group and were more likely to be White (Table 1). HCT recipients were also more likely to be

Table 1. Study Population and Isolate Characteristics (First Culture), Including Hematopoietic Stem Cell Transplant Recipients With Cultures Obtained Only After Transplant (First Transplant)

Characteristic	Non-HCT Population (n = 52 067)	HCT Population (n = 271)
Age, y, median (IQR)	61.0 (42–75)	60.0 (52.5–66)
Sex		
Male	12 654 (24.3)	119 (43.9)
Race		
White	32 391 (62.2)	205 (77.1)
Black	13 433 (25.8)	56 (21.1)
Other or unknown	6241 (12.0)	5 (1.9)
Ethnicity		
Non-Hispanic	43 590 (83.7)	226 (83.4)
Hispanic	3341 (6.4)	10 (3.7)
Unknown	5136 (9.9)	35 (12.9)
Socioeconomic status		
High	12 949 (26.1)	53 (21.4)
Medium-high	13 067 (26.4)	78 (31.5)
Medium-low	12 184 (24.6)	76 (30.6)
Low	11 370 (22.9)	41 (16.5)
Isolates per patient		
1	46 069 (88.5)	228 (84.1)
2	4957 (9.5)	31 (11.4)
3	841 (1.6)	7 (2.6)
≥4	200 (0.4)	5 (1.8)
Per isolate	n = 59 445	n = 332
Specimen source		
Blood	3668 (6.2)	114 (34.3)
Respiratory	1196 (2.0)	16 (4.8)
Urine	50 269 (84.6)	185 (55.7)
Other	4312 (7.3)	17 (5.1)
Genus isolated (top 5 found)		
Escherichia	35 771 (60.2)	186 (56.0)
Klebsiella	12 294 (20.7)[a]	76 (22.9)
Enterobacter	1749 (2.9)	27 (8.1)
Citrobacter	1558 (2.6)	7 (2.1)
Proteus	5263 (8.9)	15 (4.5)
Other	2811 (4.7)	21 (6.3)
Location		
Outpatient	16 724 (28.1)	85 (25.6)
Inpatient	11 603 (19.5)	174 (52.4)
ICU	1739 (2.9)	18 (5.4)
Emergency	27 075 (45.5)	27 (8.1)
Other/unknown	2304 (3.9)	28 (8.4)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: HCT, hematopoietic stem cell transplant; ICU, intensive care unit; IQR, interquartile range.

[a]The category *Klebsiella* contains 6 isolates of "*Enterobacter-Klebsiella*" identified by the Microbiology Laboratory.

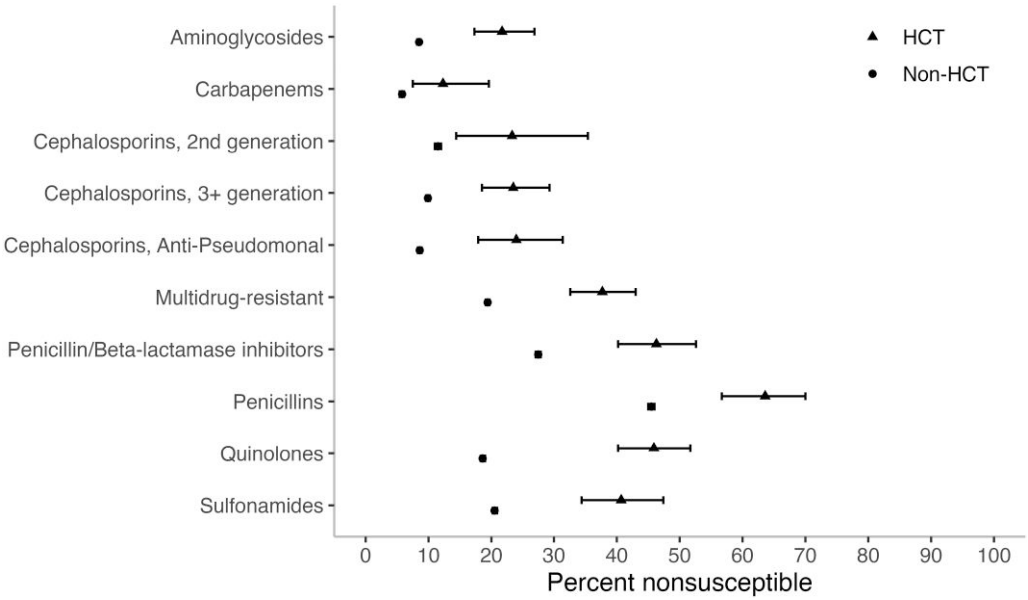

Figure 1. Percentages with 95% confidence intervals of isolates that were nonsusceptible to selected antibiotic classes or were multidrug-resistant by hematopoietic stem cell transplantation (HCT) status.

classified in the medium-high and medium-low quartiles of SES based on their ZIP code at the time a culture was obtained, compared to the non-HCT population who were more likely to be in the lowest SES quartile. Isolates of Enterobacterales were more often isolated from urine in the non-HCT population, while those from the HCT cohort were far more often from blood. The most common genera from either group were *Escherichia* and *Klebsiella*. Cultures from HCT recipients were more likely to have been obtained inpatient compared to the non-HCT population; a separate but similar comparison of patient and isolate data (non-HCT vs HCT) from only inpatient cultures is found in Supplementary Table 1.

Among HCT recipients included in the study (n = 271), the most common underlying malignancies were multiple myeloma and other plasma cell dyscrasias (Supplementary Table 2). Almost half of all HCT recipients (n = 115 [42.4%]) had undergone allogeneic transplantation (allo-HCT) and, of these, 28 patients (23.9%) developed acute graft-versus-host disease (GVHD); 8 (28.5%) patients were found to have developed grade 3 or 4 acute GVHD.

Multidrug Resistance Among Enterobacterales Isolates

The overall prevalence of MDR-E was 19.4% in the non-HCT population (95% CI, 19.1%–19.7%) and was higher among HCT recipients (37.7% [95% CI, 32.6%–43.0%]) (Figure 1). This difference in MDR-E prevalence between cohorts is even more pronounced in inpatient samples (23.1% vs 47.4%; Supplementary Figure 2). MDR-E prevalence in the non-HCT population more than doubled between 2000 and 2010 and then remained relatively stable (Figure 2*A*). The higher prevalence of MDR-E among HCT recipients was sustained across all study years, although with an observed decrease in prevalence of MDR-E after 2013–2014 (Figure 2*A*). Anti-*Pseudomonal* cephalosporin resistance also appears to have similarly peaked in the HCT cohort during the years 2013–2014 (Figure 2*B*). Overall, the MDR-E prevalence ratio comparing HCT vs non-HCT patients, adjusted for covariates (age, sex, race, SES, specimen source, location, year of culture), was 1.78 for all cultures (95% CI, 1.69–1.87) and 1.96 for only inpatient cultures (95% CI, 1.84–2.08).

Being aged >50 years was associated with a small (6%) unadjusted relative increase in MDR-E prevalence among the non-HCT population but a 36% relative decrease in MDR-E prevalence in HCT recipients (Table 2). Residing in an area with lower SES was associated with higher prevalence of MDR-E in the non-HCT population (up to a 20% unadjusted relative increase in the lowest quartile) but not in HCT recipients. Blood cultures in the HCT cohort were associated with a 68% relative increase in MDR-E prevalence compared to urine cultures but only a small 7% relative decrease in the non-HCT group. Similar comparisons were obtained for patients with inpatient cultures (Supplementary Table 3).

Among HCT recipients, undergoing autologous transplantation was associated with a 31% adjusted relative decrease in MDR-E prevalence compared to allo-HCT (Supplementary Table 4). Underlying disease was also associated with differential MDR-E risk and was highest among those with leukemia compared to lymphoma, plasma cell dyscrasias, and other hematologic malignancies. There was no significant difference in MDR-E prevalence based on whether patients undergoing

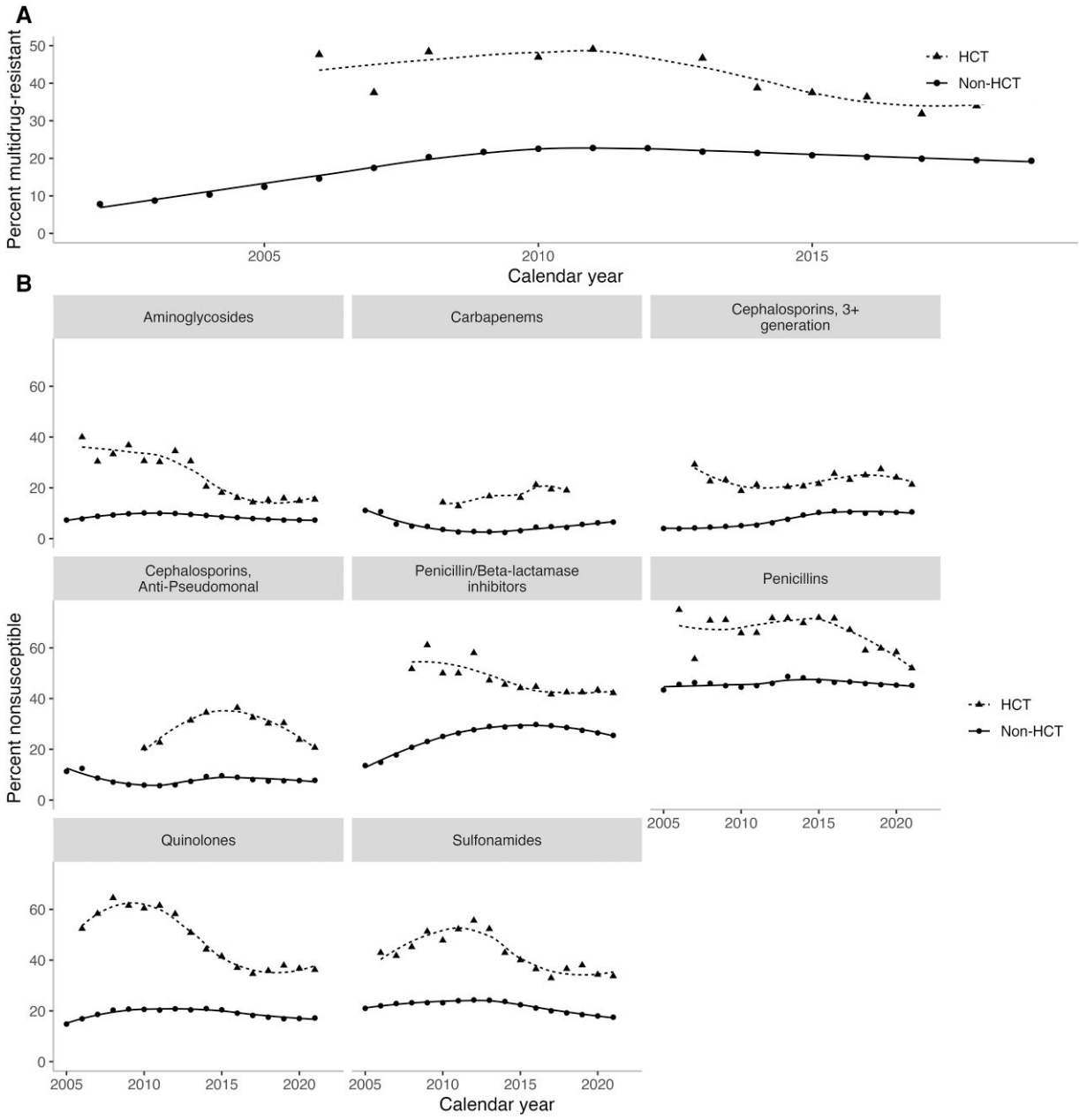

Figure 2. Five-year moving average percentage of isolates that were multidrug-resistant (*A*) or nonsusceptible to selected antibiotic classes (*B*) by calendar time and hematopoietic stem cell transplantation (HCT) status. Carbapenem resistance appears more truncated as resistance was consistently reported only after 2014.

allo-HCT developed acute GVHD or not, although this was a much smaller cohort for comparison.

Antibiotic Class Nonsusceptibility Among Enterobacterales Isolates

Among antibiotic classes, nonsusceptibility was higher in the HCT cohort compared with the non-HCT population for all antibiotic classes analyzed (Figure 1, Supplementary Figure 2). Compared with the non-HCT population, adjusted prevalence ratios for HCT recipients ranged from 1.4 to 2.1 for all antibiotic classes, with the highest prevalence ratio for aminoglycosides (2.10 [95% CI, 1.65–2.68]) and quinolones (2.05 [95% CI, 1.78–2.35]) (Table 3). The largest adjusted absolute difference in nonsusceptibility was observed for quinolones (20.4 [95% CI, 14.9–25.8]). Similar findings were observed for inpatient cultures as well (Supplementary Table 5).

All-Cause Mortality Associated With Multidrug Resistance

In our study, an accurate date of death was only available for patients who had undergone HCT. Adjusted associations between Enterobacterales resistance and all-cause mortality

Table 2. Unadjusted Associations of Covariates With Multidrug-Resistant Isolates Compared Between Non–Hematopoietic Stem Cell Transplant (HCT) and HCT Populations

Risk Factor	Non-HCT Population Prevalence Ratio (95% CI)	HCT Recipients Prevalence Ratio (95% CI)
Age, y		
>50 y	**1.06 (1.02–1.10)**	**0.64 (.48–.85)**
Sex		
Male	**1.11 (1.07–1.15)**	**1.49 (1.13–1.97)**
Race		
White (reference)	…	…
Black	1.03 (.99–1.07)	1.32 (.97–1.78)
Specimen source		
Urine (reference)	…	…
Respiratory	**1.36 (1.24–1.50)**	1.45 (.80–2.63)
Blood	**0.93 (.87–1.00)**	**1.68 (1.27–2.23)**
SES (quartiles)		
High (reference)	…	…
Medium-high	1.01 (.96–1.06)	0.84 (.54–1.32)
Medium-low	**1.14 (1.08–1.19)**	1.27 (.84–1.90)
Low	**1.20 (1.15–1.26)**	1.21 (.77–1.92)
Location		
Outpatient (reference)	…	…
Inpatient	**1.24 (1.19–1.29)**	1.61 (.88–2.94)
ICU	**1.49 (1.38–1.62)**	1.87 (.92–3.83)

Bold indicates significance, $P < .05$.

Abbreviations: CI, confidence interval; HCT, hematopoietic stem cell transplant; ICU, intensive care unit; SES, socioeconomic status.

were observed for many antibiotic classes at 1 year following MDR-E (aminoglycosides, 3+ generation and anti-pseudomonal cephalosporins, quinolones, and sulfonamides) but not at 90 days with the exception of 3+ generation cephalosporins (Table 4). HCT recipients with MDR-E demonstrated significantly reduced survival over time compared to those without MDR-E (Figure 3).

DISCUSSION

In a large population of patients seeking care at UNC from 2000 to 2023, patients undergoing HCT had a substantially higher relative prevalence of MDR-E and nonsusceptibility to all antibiotics compared to patients in the non-HCT population. Our study is the first to longitudinally compare specific antimicrobial nonsusceptibility and MDR-E prevalence between the HCT and non-HCT populations. These data highlight the importance of identifying factors that contribute to AMR; this is especially important given the potential clinical consequences of MDR pathogens. In our study, we observed significantly higher all-cause mortality associated with MDR in patients undergoing transplantation: HCT patients with MDR-E cultures after transplantation were found to have double the risk of 1-year all-cause mortality compared to patients with non-MDR-E. Preventing MDR infections posttransplantation is likely critical to reducing nonrelapse mortality following HCT.

While we observed rising rates of MDR-E from 2000 through 2010 followed by relative stability through 2023 in the non-HCT cohort, rates of MDR-E in the HCT population peaked from 2013 to 2014 and then subsequently declined. Although wider fluctuations in reported MDR-E would be expected in the smaller HCT population, the decline is quite dramatic. This period of time was concurrent with multiple published studies demonstrating the negative impact of anaerobically active antibiotics on gut microbiome diversity [19–22], and the association of low gut microbial diversity with increased incidence of acute GVHD and GVHD-related mortality [23, 24]. The extent to which purported factors alone or in combination directly impacted AMR remains speculative but is an important topic for future research.

Not surprisingly, in the HCT population, we observed higher resistance to antibiotic classes commonly used for prophylaxis or empiric neutropenic fever treatment in patients with hematologic malignancies. These include both the anti-*Pseudomonal* cephalosporins that are first-line treatment for neutropenic fever at our institution, as well as fluoroquinolones that are first-line prophylaxis during neutropenia. A similar high burden of nonsusceptibility was observed for every antibiotic class evaluated, including carbapenems, in which HCT recipients had a 135% higher relative prevalence of carbapenem-resistant Enterobacterales (CRE). Despite being higher than the non-HCT population, the relative prevalence of CRE in HCT

Table 3. Adjusted Associations Between Hematopoietic Stem Cell Transplantation and an Isolate With Nonsusceptibility to Selected Antibiotic Classes for Each Isolate

Antibiotic Class	Referent Prevalence in General Non-HCT Population (per Isolate)	Prevalence Ratio (95% CI)	Prevalence Difference (95% CI)
Aminoglycosides	7.8	**2.10 (1.65–2.68)**	**9.5 (5.1–13.9)**
Carbapenems	5.4	1.35 (.80–2.28)	2.7 (−3.5 to 8.9)
Cephalosporins, 2nd generation	11.0	**1.70 (1.01–2.87)**	8.0 (−2.1 to 18.1)
Cephalosporins, 3+ generation	9.4	**1.58 (1.24–2.02)**	**7.0 (2.0–12.0)**
Anti-pseudomonal cephalosporins	8.0	**1.79 (1.34–2.40)**	**9.2 (2.9–15.5)**
Penicillin	45.2	**1.36 (1.21–1.51)**	**16.4 (9.6–23.2)**
Penicillin + β-lactamase inhibitor	26.2	**1.68 (1.45–1.94)**	**17.3 (11.1–23.4)**
Quinolones	17.8	**2.05 (1.78–2.35)**	**20.4 (14.9–25.8)**
Sulfonamides	19.4	**1.83 (1.56–2.16)**	**17.3 (11.1–23.5)**
Multidrug resistance	19.5	**1.78 (1.69–1.87)**	**17.7 (15.6–19.8)**

Associations are adjusted for age, sex, race, specimen source, socioeconomic status, location, and year of collection.

Bold indicates significance, $P < .05$.

Abbreviations: CI, confidence interval; HCT, hematopoietic stem cell transplant.

Table 4. Adjusted Associations Between 90-Day and 1-Year All-Cause Mortality in Patients Undergoing Hematopoietic Stem Cell Transplantation

Antibiotic Class	Risk Ratio for 90-d All-Cause Mortality (95% CI)	Risk Ratio for 1-y All-Cause Mortality (95% CI)
Aminoglycosides	0.74 (.36–1.50)	**1.56 (1.05–2.31)**
Carbapenems	1.57 (.68–3.63)	1.48 (.89–2.46)
Cephalosporins, 2nd generation	0.43 (.12–1.61)	0.54 (.22–1.31)
Cephalosporins, 3+ generation	**2.00 (1.09–3.66)**	**2.38 (1.60–3.54)**
Anti-pseudomonal cephalosporins	1.96 (.91–4.20)	**2.57 (1.48–4.46)**
Penicillin	1.52 (.51–4.51)	2.03 (.95–4.35)
Penicillin + β-lactamase inhibitor	0.89 (.49–1.60)	1.46 (.98–2.20)
Quinolones	1.66 (.91–3.02)	**1.84 (1.22–2.78)**
Sulfonamides	1.78 (.89–3.53)	**2.25 (1.41–3.58)**
Multidrug resistance	1.17 (.67–2.06)	**1.98 (1.34–2.91)**

Associations are adjusted for age, sex, race, specimen source, socioeconomic status, location, and year of collection.

Bold indicates significance, $P < .05$.

Abbreviation: CI, confidence interval.

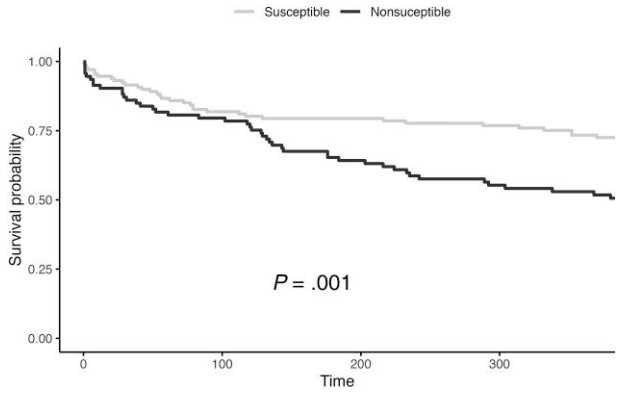

Figure 3. Kaplan-Meier analysis demonstrating increased mortality over time (in days) in hematopoietic stem cell transplant recipients with multidrug-resistant Enterobacterales infections.

recipients was lower than previously published for many geographical regions [10], although most prior publications have restricted reporting of CRE prevalence in HCT to bloodstream infections only [9, 25] or only within specific organisms such as *Klebsiella* [26]. At the same time, resistance to aminoglycosides was also much higher in the HCT population despite infrequent use at UNC and elsewhere; reasons for this difference are unclear.

Strengths of this study include the large comprehensive cohort of patients with Enterobacterales cultures over a 23-year period, inclusive of all patients undergoing HCT at UNC. In restricting our analyses to the same locations where HCT recipients had been seen, we were able to minimize selection bias in our cohort. Although locations differed between non-HCT and HCT cohorts, subsequent sensitivity analyses inclusive of only inpatient cultures demonstrated similar results. All susceptibility results were verified, and changes in CLSI cutoffs were also incorporated so that all designations of resistance or sensitivity were up to date with the most current standards. Additionally, we ensured that clinical cultures identified in the HCT cohort occurred only after HCT, thereby addressing the impact of transplantation on the prevalence of resistant Enterobacterales. As with any study, our results are subject to several limitations, including the possibility of unmeasured confounding. Laboratory practices and testing for antibiotics also changed over the 2-decade study period, as is the case with testing for carbapenems, which would have occurred less frequently in the early 2000s. All patients in the HCT cohort were obtained from a UNC database of HCT recipients; however, we did not account for patients at UNC who received transplant elsewhere. Such an occurrence would only serve to reduce the differences observed between

groups and would have minimal impact in this large cohort. We also did not account for Enterobacterales cultures obtained outside of UNC Health by HCT recipients, as many live far from any UNC hospital and may have presented locally outside of the 100 days posttransplantation when patients are required to remain close to UNC. Our study did not limit the time period between transplantation and culture, and patients with transplants who were no longer on immunosuppression many years after HCT may have been included in the cohort. This again would be expected to decrease the observed differences between groups. In addition, our study did not obtain data on the antibiotics patients received, which would have allowed for better tracking of temporal associations between antibiotic use and MDR-E incidence. Finally, we were limited to patients being treated at a single health system in North Carolina and results may not generalize beyond this geographic region.

In summary, our data demonstrate that both MDR-E and general Enterobacterales AMR prevalence were consistently higher among HCT recipients over time compared with the non-HCT population. Further investigation into risk factors for MDR-E and antibiotic nonsusceptibility will inform better approaches to prevent infections with resistant organisms and may improve overall clinical outcomes for all patients.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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