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Antimicrobial-resistant Enterobacterales colonization in people with HIV

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Background: People with HIV (PWH) may be at increased risk for MDR Enterobacterales (MDR-E) infection or colonization, relative to individuals without HIV, due to a greater burden of comorbidities as well as HIV-related intestinal inflammation and microbiota alterations.

Objectives: To characterize antibiotic susceptibility of enteric Enterobacterales and risk factors for antimicrobial-resistant bacterial infections in a sample of PWH attending routine clinic visits.

Methods: Participants provided self-administered rectal swabs and completed questionnaires regarding healthcare, travel and occupational exposures for the prior 12 months. Rectal samples were processed to identify Enterobacterales species, and susceptibility testing was performed.

Results: Among 82 participants, 110 Enterobacterales isolates were obtained. Non-susceptibility was common for penicillins, sulphonamides and first-generation cephalosporins. MDR-E was present in 20% of participants. HIV-related characteristics, including current or nadir CD4 cell count, viral suppression, or AIDS-defining clinical conditions, were not associated with MDR-E.

Conclusions: MDR-E colonization is common in this population of PWH. Further research evaluating risk factors for MDR-E in PWH may inform infection prevention approaches to better protect at-risk populations from these difficult-to-treat infections.

Introduction

MDR Enterobacterales (MDR-E) are a frequent cause of both community-associated and nosocomial infections, which are difficult to treat and associated with poor outcomes.[1] Clinically important subtypes of MDR-E include carbapenem-resistant Enterobacterales and ESBL-producing Enterobacterales, classified by the US CDC as urgent and serious threats, respectively.[2] Several known risk factors for colonization and infection with MDR-E may be more common in people with HIV (PWH), including healthcare and antibiotic exposure. In addition, specific risk factors for acquisition and prolonged carriage of MDR-E such as HIV-associated gut microbiome changes and intestinal inflammation may result in higher MDR-E prevalence in PWH.[3,4]

Prior studies, conducted by our group and others, suggest PWH may have a higher prevalence of MDR-E infection or colonization relative to individuals without HIV.[5–11] This prospective study was designed to further characterize prevalence and risk factors for MDR-E intestinal colonization among PWH.

Materials and methods

This study was based in the University of North Carolina (UNC) Center for AIDS Research HIV Clinical Cohort (UCHCC), which has enrolled all PWH aged 18 years or older receiving HIV care at the UNC Infectious Diseases Clinic since 1996.[12] For this study we co-enrolled a convenience sample of 82 PWH participating in the UCHCC with a clinical HIV visit from September 2019 through March 2020. The protocol for this study and the UCHCC were approved by the UNC Office of Human Research Ethics/Institutional Review Board.

Consecutive patients were approached during routine visits in the UNC Infectious Diseases Clinic. Individuals who provided written informed consent were screened using standard-of-care methods, including a self-administered rectal swab (ESwab, Becton Dickinson, Sparks, MD, USA). Participants also completed a self-administered

Table 1. Demographic and clinical characteristics and detected Enterobacterales isolates, stratified by multidrug resistance, among 82 persons with HIV

	MDR-E		
	absent (*N*=66)	present (*N*=16)	Prevalence difference (95% CI)
Age (years)	53 (39, 59)	49 (33, 54)	
<50			Referent
≥50	37 (56.1)	7 (43.8)	−7.8 (−25.1, 9.6)
Gender			
Cis-man	43 (65.2)	13 (81.2)	10.2 (−9.2, 29.5)
Cis-woman	20 (30.3)	3 (18.8)	Referent
Trans-man	1 (1.5)	0 (0.0)	NA
Trans-woman	2 (3.0)	0 (0.0)	NA
Race			
Black/African American	42 (63.6)	13 (81.2)	10.6 (−9.0, 30.2)
White	20 (30.3)	3 (18.8)	Referent
American Indian/Native Alaskan	2 (3.0)	0 (0.0)	NA
Other	2 (3.0)	0 (0.0)	NA
Men who have sex with men[a]	34 (51.5)	10 (62.5)	6.9 (−10.4, 24.3)
Current CD4 cell count (cells/mm^3)[b]	682 (411, 950)	656 (443, 926)	
<500			4.0 (−14.4, 22.5)
≥500			Referent
Nadir CD4 cell count (cells/mm^3)	221 (85, 476)	248 (89, 386)	
<200			0.4 (−17.3, 18.2)
≥200			Referent
Number of comorbidities[b]	2 (0, 3)	1.5 (0.75, 2.25)	NA
Healthcare exposures[a,b]			
Any	39 (59.1)	10 (62.5)	2.2 (−15.5, 19.9)
Antibiotic	26 (39.4)	4 (25.0)	−9.7 (−27.6, 8.2)
Hospitalized	21 (31.8)	5 (31.2)	−0.4 (−19.1, 18.2)
Skilled nursing facility	0 (0.0)	1 (6.2)	NA
Surgery	4 (6.1)	0 (0.0)	NA
Other procedure	7 (10.6)	2 (12.5)	NA
Urinary catheter	4 (6.1)	0 (0.0)	NA
Pregnancy	1 (1.5)	0 (0.0)	NA
International travel[b]	1 (1.5)	1 (6.2)	NA
Occupational exposure[a,b]			
Any	12 (18.2)	5 (31.2)	12.5 (−8.8, 33.7)
Hospital	2 (3.0)	0 (0.0)	NA
School	0 (0.0)	2 (12.5)	NA
Elder care	5 (7.6)	0 (0.0)	NA
Childcare	3 (4.5)	2 (12.5)	NA
Food	8 (12.1)	2 (12.5)	NA

NA, not applicable (estimate not possible due to small numbers).

Results are presented as *N* (%) or median (IQR).

[a]For characteristics without referent listed in the table, the referent is participants without the listed characteristic (e.g. men who have sex with men in contrast to participants who are not men who have sex with men; healthcare exposure 'any' in contrast to participants reporting no healthcare exposures).

[b]Characteristics represent presence in 12 months prior to sample collection.

questionnaire focused on MDR-E risk factors within the prior 12 months, including antibiotic exposures, healthcare and occupational exposures, and international travel. From the UCHCC study, we extracted data collected from the UNC electronic health record (EHR) on demographics (age, sex, race and ethnicity) and medical history (nadir and most recent CD4 count, diagnosis codes for co-morbid conditions, antibiotic prescriptions and hospital admissions).

Comorbidities were classified using ICD-10 diagnosis codes for diagnoses within the 12 months prior to study enrolment. ICD-10 diagnosis codes were grouped into clinically meaningful categories using Agency for Healthcare Research and Quality Clinical Classification Software.[13] Participant antibiotic exposures and hospitalizations were defined as present in the prior 12 months if documented in the UCHCC data or reported on the participant questionnaire.

Rectal swabs were vortexed, plated on MacConkey agar, and incubated overnight at 35°C. Organisms were identified using MALDI-TOF MS (VITEK MS, bioMérieux, Durham, NC, USA). Kirby–Bauer disc diffusion was performed according to CLSI guidelines for ampicillin, ampicillin/sulbactam, cefazolin, cefepime, ceftriaxone, ertapenem, gentamicin, levofloxacin, meropenem, piperacillin/tazobactam, tobramycin and trimethoprim/sulfamethoxazole using interpretations from the M100-S29.[14,15] We classified an isolate as non-susceptible to an antibiotic class if it had a susceptibility test result of intermediate or resistant to at least one member of the class, after removing results corresponding to intrinsically resistant species–antibiotic combinations (e.g. *Klebsiella pneumoniae* and ampicillin). Isolates that were non-susceptible to three or more antibiotic classes were classified as MDR.

We performed standard descriptive analyses of susceptibility testing results, as well as participant questionnaire responses and demographic and clinical data. To assess the association of MDR-E with participant characteristics, we estimated prevalence differences (PD) and 95% CI. All analyses were performed using R (version 4.1.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 82 participants were enrolled, of whom 28% were cis-women, 68% were cis-men and 4% were trans-men/women (Table 1). Completed questionnaires and the selected variables from the EHR from the 12 months prior to enrolment were obtained for all. Participants were predominantly black (67%) and more than one-half were men who have sex with men (54%). The median age was 53 years (IQR 36, 58). All but three participants (96%) had undetectable HIV RNA levels. The median nadir and current CD4 cell counts were 237 cells/mm^3 (IQR 85, 476) and 682 (IQR 418, 950), respectively. Participants had a median of two comorbidities, and 12 (15%) had a diagnosis of an AIDS-defining clinical condition within the previous 12 months. Twenty-six (32%) participants had self-reported or EHR evidence of antibiotic exposure in the 12 months prior to enrolment, and 21 (26%) had been hospitalized.

Enterobacterales were cultured from 68/82 (83%) participants, with up to 4 isolates obtained per participant (110 total isolates). The majority of isolates were *Escherichia coli* (82/110, 75%), followed by *K. pneumoniae* (10/110, 9%) and *Proteus mirabilis* (5/110, 5%). Non-susceptibility was most common for penicillins (42/92, 46%), followed by sulphonamides (38/110, 35%) and first-generation cephalosporins (33/105, 31%). Multidrug resistance was present in 23/110 (21%) of isolates and in 16/82 (20%) of participants. Multidrug resistance was only observed in *E. coli* isolates (23/82; 28%).

Median CD4 cell count nadir was similar between participants with and without MDR-E (248 and 221 cells/mm^3, respectively). Likewise, current CD4 cell count was similar between those with and without MDR-E (656 and 682 cells/mm^3, respectively). Of the three participants with detectable HIV RNA level, one was severely immunocompromised and had a current prescription for trimethoprim/sulfamethoxazole; none of these three participants had MDR-E isolated.

Participants with evidence of antibiotic exposure in the previous 12 months had a lower prevalence of MDR-E relative to those without evidence of antibiotic exposure (PD: −9.7 [95% CI: −27.6, 8.2]). We found no association between exposure to any individual antibiotic class in the prior 12 months and having an isolate that was non-susceptible to that antibiotic class. Comparing participants with, versus without, hospitalization in the previous 12 months, there was no difference in MDR-E prevalence (PD: −0.4 [95% CI: −19.1, 18.2]). Participants with an occupational risk factor (i.e. worked in a hospital, skilled nursing facility, elder care, school, childcare or food service setting) in the previous 12 months had a higher prevalence of MDR-E (PD: 12.5 [95% CI: −8.8, 33.7]).

Discussion

MDR-E colonization was common in this convenience sample of 82 PWH receiving routine HIV care between September 2019 and March 2020 in a large tertiary care centre in the southeastern USA. The results of this prospective study are consistent with those of our prior retrospective study[9] of clinical isolates among PWH, as well as those reported by Reinheimer *et al.*[8] in a retrospective study of MDR Gram-negative colonization in 109 men with HIV in Germany. In the Reinheimer *et al.*[8] study, participants were hospitalized, with a large proportion having CD4 cell counts <500 cells/mm^3, whereas our participants were typically virally suppressed, with CD4 cell counts >500 cells/mm^3.

A high proportion of isolates in this study were non-susceptible to sulphonamides (35%). In our retrospective study, we found that sulphonamide non-susceptibility was significantly more prevalent among clinically obtained Enterobacterales isolates from PWH compared with individuals without HIV (31% and 20%, respectively).[9] Furthermore, the prevalence did not decline during the 2000–18 study period, although use of trimethoprim/sulfamethoxazole prophylaxis decreased during that time as a result of improvements in antiretroviral therapies. Trimethoprim/sulfamethoxazole has long been used to prevent opportunistic infections in PWH with low CD4 cell counts; however, we did not find an association between previous trimethoprim/sulfamethoxazole prescriptions or self-reported trimethoprim/sulfamethoxazole exposure and having a sulphonamide-non-susceptible Enterobacterales in our participants. The apparent lack of association between trimethoprim/sulfamethoxazole exposure and sulphonamide non-susceptibility in Enterobacterales could be due a number of factors, including possible additional drivers of resistance (i.e. indirect effects of other antibiotics or spread of a stable resistant phenotype). In addition, HIV-related gut inflammation may increase the likelihood of transmission of Enterobacterales among PWH.

This study is the first to prospectively characterize Enterobacterales colonization among PWH in the USA. A strength of the study is the availability of data from a long-standing, well-characterized clinical cohort. However, there are several limitations. Participants were selected as a convenience sample from a single clinic, the sample size is small, and there was little variation in HIV-related clinical characteristics as most were virally suppressed. Thus, the results may not be generalizable. Comparisons between participants with, versus those without, MDR-E are difficult to interpret due to imprecise estimates. Further, no comparison group of individuals without HIV was available to evaluate whether prevalence of MDR-E colonization and risk factors differ between individuals with versus without HIV. Actual antibiotic exposures could not be verified, as presence of a prescription in the EHR does not prove that an antibiotic was taken by a patient. Participants may have received care outside of

the UNC Health system, in which case hospital admissions, antibiotic prescriptions and diagnoses would not be available in the EHR; however, we were able to include self-reported data on antibiotic usage and hospitalizations.

These findings suggest that MDR-E colonization is common among PWH receiving care at the UNC Infectious Diseases Clinic. Further research evaluating risk factors for MDR-E infections and colonization in PWH may inform infection prevention approaches to better protect at-risk populations from these difficult-to-treat infections.

Funding

Transparency declarations

None to declare.

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