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Co-Colonization with Multiple Different Species of Multidrug-Resistant Gram-Negative Bacteria

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Abstract

Background—The characteristics of co-colonization with multiple different species of multidrug-resistant gram-negative bacteria (MDRGN) have not been fully elucidated. Quantifying the prevalence of co-colonization and those patients at higher risk of co-colonization may have important implications for strategies aimed at limiting the spread of MDRGN.

Methods—To determine the prevalence of MDRGN colonization, rectal swabs were obtained from 212 residents residing in a 600-bed long-term care facility. Co-colonization was defined as colonization with ≥ 2 different MDRGN species. Co-colonized residents were compared to residents colonized with a single MDRGN species to identify factors associated with an increased risk for co-colonization. Molecular typing was performed to determine the contribution of cross-transmission to the co-colonized state.

Results—A total of 53 (25%) residents were colonized with ≥ 1 MDRGN. Among these, 11 (21%) were colonized with ≥ 2 different species of MDRGN. A global deterioration score of ≥ 5 representing advanced dementia and an increased requirement for assistance from healthcare workers, was significantly associated with co-colonization ($P = 0.05$). Clonally-related MDRGN strains were identified among 7 (64%) co-colonized residents.

Conclusions—The prevalence of co-colonization with ≥ 2 different MDRGN is substantial. Cross-transmission of MDRGN is a major contributor to the co-colonized state.

INTRODUCTION

Infections caused by multidrug-resistant gram-negative bacteria (MDRGN) are associated with considerable morbidity and mortality and continue to increase in frequency.^{1–7} Studies have begun to elucidate the characteristics of MDRGN colonization by describing prolonged duration of colonization for up to five months,^{8,9} co-colonization with multiple different strains of the same gram-negative bacterial species,¹⁰ and co-colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE).^{11–15} Mechanisms of acquisition of MDRGN include patient-to-patient spread and transfer of

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resistance genes between different gram-negative bacterial species within an individual's gastrointestinal tract.^{16–19} The potential to acquire MDRGN both exogenously and endogenously suggests that patients may have a substantial risk of becoming colonized with more than one different MDRGN species. Understanding the epidemiology of MDRGN co-colonization would have important implications for preventive efforts aimed at limiting their spread.

A clinical and molecular epidemiological investigation was performed to quantify the prevalence of MDRGN co-colonization and to identify unique characteristics of patients at higher risk of co-colonization. To understand the contribution of cross-transmission to co-colonization, clonally-related MDRGN strains were identified using pulsed-field gel electrophoresis (PFGE).

METHODS

Study design

This study was conducted at the Hebrew Rehabilitation Center for the Aged, a 600-bed, 15-unit long-term care facility (LTCF) in Boston, Massachusetts. During the time period of October 31, 2006 through October 22, 2007, 212 residents on 4 of 15 units of the facility participated in an infection control initiative targeting MDRGN. Data regarding voluntary patient participation in this study population has been described previously.²⁰ The four discrete units were chosen as they represented a variety of acuity levels at the facility and a range of functional and cognitive abilities among the residents. Patient room assignment changes very infrequently, although nearly all patients are brought to common spaces daily. Data on a subset of this cohort of residents including risk factors for colonization with at least one MDRGN and transmission patterns have been previously published.²⁰ The conduct of this study was approved by the institutional review board at the study institutions, including a waiver of consent for review of collected microbiologic isolates and clinical variables.

Data Collection

Rectal swabs were obtained on all participating residents at the time of enrollment over the 12-month study period. Clinical variables potentially associated with MDRGN co-colonization were collected from the medical record at the time of enrollment. Demographic variables included age, gender and race. Healthcare-associated variables included duration of admission to the LTCF, ward and room location, and hospitalization and antimicrobial use in the preceding 12 months. Antimicrobial use was defined as receipt of any enteral or parenteral antimicrobial agent. Health, functional, and cognitive status variables included resuscitation status, the presence of a pressure ulcer, fecal incontinence documented by a physician, Charlson index as a composite of score of comorbid conditions,²¹ and global deterioration score (GDS). The GDS is a validated assessment of dementia for which a score of 1 represents no cognitive decline, and higher scores represent progressively greater degrees of dementia. Scores of 5, 6 and 7 represent moderately severe, severe, and very severe cognitive decline, respectively, for which patients require assistance with activities of daily living.²² In this study the GDS score was therefore dichotomized at ≥ 5 , representing a group of residents requiring increased assistance from healthcare workers.

Microbiological methods

Swabs were processed for MDRGN using McConkey media supplemented with 2 $\mu\text{g/mL}$ of ciprofloxacin or 2 $\mu\text{g/mL}$ of ceftazidime in order to minimize the recovery of pan-susceptible gram-negative bacteria. MDRGN species identification, antibiotic susceptibility testing and determination of genetic relatedness by PFGE were performed as previously

described.⁸ Indistinguishable or closely related strains, defined as strains differing by ≤ 3 bands, were considered clonally related.²³

Definitions

Co-colonization with MDRGN was defined as colonization with ≥ 2 different MDRGN species. MDRGN were defined as isolates resistant or intermediately susceptible to three or more of the following antimicrobials or antimicrobial classes: beta-lactam/beta-lactamase inhibitor combinations (ampicillin/sulbactam, piperacillin/tazobactam), third- or fourth-generation cephalosporins, meropenem, ciprofloxacin, and gentamicin.

Statistical Methods

To determine potential factors associated with co-colonization, characteristics of residents colonized with ≥ 2 different MDRGN species were compared to residents colonized with a single MDRGN species. Ordinal variables were dichotomized at a clinically appropriate cut-off and continuous variables were dichotomized at the mean. Statistical difference in variables was assessed using the Fisher's exact test. Variables with a $P < 0.1$ were included in a stepwise logistic regression model. Statistical analysis was performed using Stata software, version 10.0 (StataCorp, College Station, TX).

RESULTS

Prevalence of co-colonization

Of the 212 residents participating in the study, 53 (25%) were colonized with one or more different species of MDRGN. Details regarding colonization with at least one MDRGN species have been previously published.²⁰ Among the 53 colonized residents, 11 (21%) were colonized with two or more different MDRGN species. Ten and 1 residents were colonized with 2 and 3 different MDRGN species, respectively. MDRGN species among co-colonized residents included: *Klebsiella pneumoniae* (6 isolates), *Proteus mirabilis* (5), *Escherichia coli* (4), *Providentia stuartii* (4), *Morganella morganii* (3), and *Citrobacter freundii* (1).

Risk factors for co-colonization

Demographic and clinical variables among co-colonized and singly-colonized residents are presented in Table 1. The median age for all residents was 87 years (interquartile range, 82–93 years) and the mean duration of LTCF admission was 3.5 years (interquartile range 0.4–5.6 years). A GDS score ≥ 5 was the only statistically significant variable: among the 11 residents co-colonized with MDRGN, all 11 (100%) had a GDS score ≥ 5 , compared to 30 (71%) singly-colonized residents ($P=0.05$). Logistic regression analysis was not performed since only one variable was statistically significant on bivariate analysis.

Antimicrobial susceptibility profile and PFGE

Only two resident pairs of isolates had an identical tested susceptibility profile, including *E. coli* and *P. stuartii*, and *P. mirabilis* and *M. morganii*. All four organisms were resistant to resistant to ampicillin/sulbactam, ciprofloxacin, and gentamicin. No species-species pair was represented more than twice. Isolates were most commonly resistant to ampicillin/sulbactam and ciprofloxacin (22 of 23 isolates each) and least commonly resistant to piperacillin/tazobactam and meropenem (5 of 23 isolates each). The PFGE patterns for 5 of 6 *K. pneumoniae* isolates were indistinguishable or closely related (Figure 1). Four of these residents resided on the same unit. All four isolates of *P. stuartii* were genetically indistinguishable. These four residents resided on two different units (two residents per ward). The PFGE pattern for *P. mirabilis*, *E. coli*, and *M. morganii* isolates differed by ≥ 6

bands and were considered genetically unrelated (data not shown). Two co-colonized residents were colonized with identical *K.pneumoniae* and *P.stuartii* strains, therefore 7 (64%) of 11 co-colonized residents harbored clonally-related strains. None of the 11 co-colonized residents shared a room contemporaneously.

DISCUSSION

This study quantified the prevalence of and risk factors for colonization with multiple different MDRGN species among residents in a LTCF. A total of 21% of residents colonized with MDRGN were co-colonized with 2 or more different MDRGN. Residents with advanced dementia, requiring increased assistance from healthcare workers, were at higher risk of MDRGN co-colonization. This finding coupled with the presence of clonally-related MDRGN strains among the majority of co-colonized residents suggests that cross-transmission between patients may increase the risk of co-colonization.

The results of this study extend the knowledge of MDRGN colonization and highlight important characteristics of co-colonization that warrant consideration when implementing strategies aimed at limiting MDRGN spread. Current guidelines from the Centers for Disease Control and Prevention for limiting the transmission of multidrug-resistant organisms recommend active surveillance cultures to detect asymptomatic colonization in some settings, especially if other control measures are insufficient.²⁴ In the specific case of carbapenem-resistant *Enterobacteriaceae*, more aggressive infection control interventions are recommended including active surveillance cultures for patients with epidemiological links to colonized or infected patients and point-prevalence surveys in high-risk units.²⁵ The high rate of MDRGN co-colonization, present among 1 in 5 colonized patients in this study, emphasizes the importance of ensuring that all potential MDRGN are identified from surveillance cultures. Failure to detect all MDRGN species would result in inaccurate point-prevalence estimates and would potentially miss epidemiological links between patients. Moreover, if co-colonization with different MDRGN species is not detected, inappropriate cohorting among patients colonized with MDRGN may result. Given the absence of standardized and selective screening culture media for MDRGN, the increased cost and labor associated with processing surveillance cultures for all MDRGN will need careful consideration.

In this study, patients with advanced dementia and who therefore required increased assistance from healthcare workers were at a significantly higher risk of co-colonization with MDRGN. Patients who are colonized with multiple different MDRGN species may be at increased risk of spreading MDRGN compared to patients colonized with only one MDRGN species. Determining whether co-colonized patients are the “superspreaders” of MDRGN requires further investigation since this subset of patients may require more aggressive infection control interventions.

Cross-transmission of MDRGN is one of the main mechanisms of MDRGN acquisition.^{16, 20, 26, 27} In this study, clonally-related MDRGN strains were identified between the majority of co-colonized residents, implying that patient-to-patient transmission contributes substantially to co-colonization. While the mobility of the patients enrolled in this study is limited and not significantly associated with co-colonization, at this facility patients do typically have daily social interactions in common areas which may provide an opportunity for MDRGN transmission. In a recent study of this population, nearly 8% of healthcare workers were carriers of MDRGN and less than 2% of environmental samples from the facility’s common areas were positive for MDRGN, while 23% of residents included in the point-prevalence survey were colonized with MDRGN.²⁰ Although this study did not address mechanisms of resistance or horizontal gene transfer, the lack of similar

antimicrobial susceptibility profiles among co-colonizing strains suggests that horizontal gene transfer did not contribute to co-colonization. Future studies with a larger patient population are needed to adequately compare the relative contribution of exogenous versus endogenous acquisition to MDRGN co-colonization.

Co-colonization with different antimicrobial-resistant bacteria, including VRE, MRSA, and single-drug resistant gram-negative bacteria, has been well-documented with prevalence percentages ranging from 1–11%.^{11, 13, 28–30} Rates of co-colonization with multidrug-resistant *Acinetobacter* spp. and extended-spectrum β -lactamase-producing gram-negative bacteria are even higher, documented in up to 38% of patients.³¹ Co-colonization in these studies likely represents the commonality of risk factors among patients harboring antimicrobial-resistant bacteria, including advanced age, antimicrobial and hospital exposure, residing in a LTCF, and other factors promoting acquisition through patient-to-patient spread.³² In this study, the clonal dissemination of MDRGN strains in a subset of patients requiring increased healthcare worker assistance, lends further support to the commonality of risk factors for colonization with antimicrobial-resistant bacteria.

There are several limitations in this study that warrant consideration. The study was conducted in a LTCF which may limit generalizability to other healthcare settings, such as acute-care facilities. The study sample size was small and therefore the study may be underpowered to detect other statistically significant variables associated with an increased risk of co-colonization. Use of media supplemented with ciprofloxacin or ceftazidime may have increased the recovery of MDRGN resistant to these antimicrobials. Lastly, identifying all potential MDRGN species from surveillance swabs is subject to microbiological technical limitations and therefore the prevalence of co-colonization may have been underestimated.

This study has begun to elucidate the epidemiology of co-colonization with multiple different MDRGN species, an important step in the ongoing effort to control the spread of these multidrug-resistant organisms. Acquisition through both endogenous and exogenous mechanisms, and co-colonization with multiple different MDRGN species will make infection control initiatives targeting MDRGN much more challenging compared to those targeting VRE and MRSA.

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Figure 1. Pulsed-field gel electrophoresis band patterns from multidrug-resistant *Klebsiella pneumoniae* isolates recovered from residents co-colonized with ≥ 2 different species of multidrug-resistant gram-negative bacteria, demonstrating indistinguishable or closely related strains (lanes 1, 2, 3, 4, 6). The M lane represents *Staphylococcus* 519 size marker, with standard band sizes labeled.

Table 1

Characteristics of residents singly- and co- colonized with multidrug-resistant gram-negative bacteria in a long-term care facility.

Variable	Number of residents (%):		OR (95% CI)	P value
	Singly-colonized (n=42)	Co-colonized (n=11)		
Age ≥ 87 years	21 (50)	5 (46)	0.8 (0.2–3.9)	1.0
Female gender	36 (86)	8 (73)	0.4 (0.1–3.4)	0.4
Caucasian race	39 (93)	9 (82)	0.4 (0.0–4.8)	0.3
LTCF admission duration ≥ 3.5 years	16 (38)	6 (55)	2.0 (0.4–9.4)	0.5
≥ 1 hospitalization in preceding 12 months	6 (14)	1 (9)	0.6 (0.0–6.0)	1.0
Any antibiotic use in preceding 12 months	33 (79)	9 (82)	1.2 (0.2–13.6)	1.0
Do not resuscitate status	33 (79)	8 (73)	0.7 (0.1–5.2)	0.7
Pressure ulcer present	11 (26)	4 (36)	1.6 (0.3–7.9)	0.7
Fecal incontinence	37 (88)	11 (100)	—	0.6
Non-ambulatory	34 (81)	10 (91)	2.4 (0.3–114)	0.7
Charlson index score ≥ 3	21 (50)	8 (73)	2.7 (0.5–17.5)	0.3
Global deterioration score ≥ 5	30 (71)	11 (100)	—	0.05

Note. Odds ratio, OR; confidence interval, CI; long-term care facility, LTCF. Reported p-values are two-sided.