Clinical Infectious Diseases

BRIEF REPORT

Acquisition of Multidrug-resistant Organisms in the Absence of Antimicrobials

Erika M. C. D'Agata,[1] Aby Varu,[2] Sara F. Geffert,[1] Rafael Araos,[3] Susan Mitchell,[4] Aaron Situ,[2] and Chris Cameron[2]

[1]Division of Infectious Diseases, Brown University, Providence, Rhode Island; [2]Cornerstone Research Group, Burlington, Ontario, Canada; [3]Instituto de Ciencias e Innovación en Medicina, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile; and [4]Hebrew SeniorLife Institute for Aging Research, Harvard University, Boston, Massachusetts

A nested case-control study among 137 nursing home residents who did not receive antimicrobials, of whom 44 acquired a multidrug-resistant organism, was performed. Risk factors for acquisition included gastrointestinal medications that affect the gut microbiome, number of visits from healthcare workers, pressure ulcers, and not residing in a dementia unit.

Keywords. methicillin-resistant *Staphylococcus aureus*; multidrug-resistant gram-negative bacteria; acquisition; long-term care facilities; advanced dementia.

It is undisputed that antimicrobial exposure promotes the emergence and dissemination of multidrug-resistant organisms (MDRO). However, in studies that demonstrate an association between MDRO acquisition and antimicrobial exposure, there is almost always a subset of patients who acquired MDRO but were never exposed to antimicrobials. Factors associated with MDRO acquisition in patient populations not exposed to antimicrobials have not been explored.

In the 5-year prospective Study of Pathogen Resistance and Exposure to Antimicrobials in Dementia (SPREAD), serial rectal and nasal swabs were collected quarterly for up to 12 months to determine MDRO acquisition rates among 362 residents from 35 nursing homes [1, 2]. Among these, 137 were not exposed to antimicrobials, of whom 44 (32%) acquired an MDRO. Our goal in this study was to define the patient characteristics and other potential risk factors associated with MDRO acquisition among the subset of participants not exposed to antimicrobials.

METHODS

We conducted a nested case-control study to identify risk factors associated with MDRO acquisition among residents who were not exposed to antimicrobials. The methodology of SPREAD has been detailed elsewhere [1, 2]. Patient data were abstracted from the medical chart and medication records at baseline and at 3-month intervals for 12 months or until death. At baseline and quarterly, nurses were interviewed to quantify the residents' functional status using the Bedford Alzheimer nursing severity subscale and the presence of pressure ulcers [3]. At each quarterly assessment, the number of visits from healthcare workers (HCWs), that is, a physician, nurse practitioner, or physician assistant, during the prior quarter was abstracted from the chart. Antimicrobial data were obtained from the medication records for the 30 days prior to study enrollment, at baseline, and quarterly thereafter. Gastrointestinal medications included laxatives and acid reducers, as these agents cause microbiome dysbiosis and can increase the colonization risk of MDRO and other pathogens [4].

Rectal and nasal swabs were obtained at baseline and quarterly to document colonization with MDRO, including multidrug-resistant gram-negative bacteria (MDRGN), methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (VRE). Multidrug resistance among MDRGN was defined as resistance to 3 or more of the following antimicrobials or antimicrobial classes: extended-spectrum penicillins (ampicillin/sulbactam or piperacillin/tazobactam), third-generation cephalosporins (ceftazidime or ceftriaxone), gentamicin, ciprofloxacin, and meropenem.

In the present study, we analyzed the subset of SPREAD residents who did not receive any antimicrobials from the 1 month prior to enrollment and throughout their study participation. Inclusion criteria required that at least 2 serial swabs be collected for each resident. Cases and controls were defined as patients who acquired and did not acquire an MDRO, respectively. MDRO acquisition was defined as a negative baseline swab for MDRO and 1 positive follow-up swab for MDRO from the same collection site (rectal or nasal). For those cases that were colonized at baseline with an MDRO, acquisition required the detection of a different MDRO (MRSA, VRE, or a different MDRGN species).

Differences between cases and controls were analyzed using the 2-sample Student *t* test or Wilcoxon rank-sum test for continuous variables. Categorical variables were analyzed using Pearson χ^2 test or Fisher exact test. Risk factors were identified through stepwise regression model selection. To account for time-dependent variables, the Cox regression model was used. Statistical significance testing was defined using a 2-tailed P value < .05.

RESULTS

Among 362 enrolled nursing home residents, 318 (88%) had 2 or more serial nasal or rectal swabs. Among these, 137 (43%) did not receive any antimicrobials during the study period, of

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Correspondence: E. M.C. D'Agata, Brown University, Alpert Medical School, 593 Eddy Street, Providence, RI 02903 (edagata@Lifespan.org).

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whom 44 (32%) acquired an MDRO (cases) and 93 (68%) did not acquire an MDRO (controls). Duration of follow-up for cases was on average 172 days (range, 84–372 days) and for controls was 324 days (range, 85–379 days). MDRO acquisition was detected at the 3-, 6-, 9-, and 12-month interval among 26, 8, 4, and 6 residents, respectively. For controls, 5, 9, 9, and 70 residents were followed until the 3-, 6-, 9-, and 12-month interval. Among the 44 cases, there was no antimicrobial exposure for an average of 203 days (range, 114–402 days) prior to MDRO acquisition. Baseline characteristics and other factors are shown in Table 1. In multivariable cox regression analyses, the following 4 factors were significantly associated with MDRO acquisition (adjusted hazard ratio [95% confidence interval], *P* value): not residing in a skilled care unit (2.2 [1.6–4.1], *P* = .02), number of HCW visits (2.9 [2.1–5.8], *P* = .002), presence of pressure ulcers (3.3 [2.1–7.8], *P* = .008), and receiving gastrointestinal medications (1.6 [1.4–2.3], *P* = .01). Subset Cox regression analyses of MDRGN and MRSA acquisition identified the same 4 variables, with the exception of gastrointestinal medications, which was not associated with MRSA acquisition (data not shown). There was no violation of the proportional hazard assumption or significant collinearity or interaction between variables.

A total of 57 MDRO isolates were acquired among cases: MDRGN (54%), MRSA (44%), and VRE (2%). MDRGN species included (number of isolates) *Providencia stuartii* (10), *Escherichia coli* (9), *Proteus mirabilis* (8), *Morganella morganii*

Table 1. Characteristics of Nursing Home Residents Who Acquired (Cases) and Did Not Acquire (Controls) Multidrug-resistant Organisms

Variable	Cases N = 44	Controls N = 93	*P* Value
Mean age (years) (SD)	85 (8)	88 (7)	.09
Female	39 (89%)	83 (89%)	1.0
Race or ethnic origin			
White	41 (93%)	85 (91%)	.27
Black	1 (2%)	7 (8%)	.44
Hispanic	2 (5%)	1 (1%)	.32
Other	0 (0%)	0 (0%)	1.0
Alzheimer's disease	35 (80%)	67 (72%)	.35
Bedford Alzheimer nursing severity subscale (SD)	21.9 (2.6)	21.4 (2.6)	.24
Test for severe impairment (SD)	1.7 (2.3)	1.6 (2.1)	.78
Diabetes mellitus	8 (18%)	10 (11%)	.23
Chronic obstructive pulmonary disease	3 (7%)	5 (5%)	.71
Coronary artery disease	7 (16%)	17 (19%)	.73
Gastrointestinal disease	8 (18%)	24 (26%)	.68
Size of nursing home (number of beds)			.43
0–99	0 (0%)	4 (4%)	…
100–199	25 (57%)	47 (50%)	…
>200	19 (43%)	42 (46%)	…
Years in nursing home prior to enrollment (SD)	3.5 (2.5)	3.6 (2.6)	.83
Number of hospital admissions (SD)	1 (0.1)	1 (0.1)	1.0
Not residing in a special care dementia unit	28 (64%)	39 (42%)	.02
Indwelling urinary catheter			
Mean cumulative incidence	3 (7%)	1 (1%)	.11
Percutaneous endoscopic transgastric or J tube			…
Mean cumulative incidence	2 (5%)	10 (9%)	.34
Number of visits from healthcare workers[a] (SD)			
Mean cumulative incidence	31.5 (2.6)	5.1 (1.7)	<.001
Presence of pressure ulcers	28 (64%)	13 (14%)	<.001
Receiving gastrointestinal medications	37 (84%)	58 (62%)	.02
Docusate	7 (16%)	10 (11%)	…
Lactulose	2 (5%)	4 (4%)	…
Polyethylene glycol	0 (0%)	3 (3%)	…
Senna	19 (43%)	28 (30%)	…
Bisacodyl	2 (5%)	5 (5%)	…
Omeprazole	6 (14%)	5 (5%)	…
Pantoprazole	0 (0%)	1 (1%)	…
Ranitidine	1 (2%)	2 (2%)	…

Abbreviation: SD, standard deviation.

[a]Includes physicians, nurse practitioners, and physician assistants.

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(3), and *Pseudomonas aeruginosa* (1). Among MDRGN, percent resistance was as follows: ampicillin/sulbactam and ciprofloxacin 97% each; gentamicin 87%, ceftriaxone and ceftazidime 23% each; and piperacillin/tazobactam and meropenem 10%, each.

DISCUSSION

Among a cohort of 137 nursing home residents who did not receive antimicrobials, 44 (32%) acquired an MDRO. These residents had not been exposed to antimicrobials for an average of 203 days, with an upper limit of 402 days, prior to the detection of MDRO acquisition. Factors associated with acquisition were more frequent visits from HCWs, presence of pressure ulcers, not residing in a special care dementia unit, and receiving medications that affect the gastrointestinal tract.

MDRO acquisition predominantly occurs through cross-transmission via contact with contaminated HCWs and the environment and frequently occurs in the nursing home setting. In this study, the finding of more frequent HCW visits among residents who acquired MDRO supports this mechanism of acquisition. Lending further support is the fact that MDRO acquisition was more common among residents with pressure ulcers, which require more contact with HCWs [5]. Another source of MDRO contributing to cross-transmission is the environment. Although not evaluated in this study, numerous epidemiological investigations have demonstrated the role of contaminated inanimate surfaces in MDRO acquisition [6]. Other potential environmental sources are numerous since the environmental resistome is one of the largest reservoirs of antimicrobial resistance [7]. Ingested food products, such as retail poultry, water, soil, and animals have all been shown to harbor MDRO [7].

Although there are numerous sources of MDRO, the question that arises is why did MDRO acquisition occur in the absence of antimicrobial exposure? A healthy microbiome provides colonization resistance, a term that reflects the protective effect of the commensal flora against colonization of exogenous pathogenic bacteria [8]. In this study, residents who acquired MDRO may have had a more dysbiotic microbiome compared to those who did not acquire MDRO. Supporting this hypothesis is the finding that residents who acquired MDRO had greater exposure to medications, including laxatives and acid reducers, which affect the gut microbiome and the risk of MDRO acquisition [4]. Moreover, in the subset analysis of acquisition of only MRSA isolates, which predominantly colonize the nares and not the gut, these medications were not associated with MRSA acquisition. Microbiome dysbiosis also occurs with antimicrobial exposure. Although in this study residents did not receive antimicrobials for an average of 7 months prior to MDRO acquisition, antimicrobial exposure that occurred prior to the study period may have led to dysbiosis of the microbiome, since even remote exposure can have lasting deleterious effects on the microbiome composition [9]. Last, residents who acquired MDRO were less likely to reside in special dementia care units, which are geographically separated units within nursing homes and provide care only for dementia patients from specially trained staff. The reasons for this association need further investigation.

There are several limitations that warrant discussion. First, the patient population focused on residents of nursing homes with advanced dementia; therefore, results may not be generalizable. Second, the sensitivity of the rectal swab ranges from 58% to 78% and is much lower in the absence of current antimicrobial exposure [10, 11]. Thus, the actual rate of MDRO acquisition events may have been underestimated, leading to nondifferential bias. Third, false-negative results from the initial sample among cases may not have detected MDRO colonization at baseline. However, 21 (41%) of the 44 residents who acquired MDRO had 2 or more negative swabs for MDRO prior to detecting MDRO acquisition, thereby reducing the likelihood that prior MDRO colonization was not identified.

Our findings in this study further increase the complexities involved in preventing the emergence and spread of MDRO, since MDRO acquisition can occur even in the absence of "recent" antimicrobial exposure. Along with ongoing efforts toward adherence to infection control measures, future studies are needed to further define mechanisms that contribute to MDRO acquisition in the absence of antimicrobial exposure, including the role of microbiome dysbiosis, non-antimicrobial medications, and the environment.

Notes

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