Published in final edited form as:

Infect Control Hosp Epidemiol. 2015 August ; 36(8): 930–935. doi:10.1017/ice.2015.97.

MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA: INTER- AND INTRA-DISSEMINATION AMONG RESIDENTS WITH ADVANCED DEMENTIA

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Abstract

Objective—To quantify the extent of inter- and intra-nursing home transmission of multidrug-resistant gram-negative bacteria (MDRGN) among residents with advanced dementia and characterize MDRGN colonization among these residents.

Design—Prospective cohort study

Setting—Twenty-two nursing homes in the greater Boston, Massachusetts area.

Patients—Residents with advanced dementia

Methods—Serial rectal surveillance cultures for MDRGN and residents characteristics were obtained every 3 months for 12 months or until death. Molecular typing of MDRGN isolates was performed by pulsed-field gel electrophoresis.

Results—A total of 190 MDRGN isolates from 152 residents with advanced dementia were included in the analyses. Both intra- and inter-nursing home transmission were identified. Co-colonization with more than one different MDRGN species occurred among 18.4% of residents. A total of 168 (88.4%), 20 (10.5%) and 2 (1%) of MDRGN isolates were resistant to three, four and five different antimicrobials or antimicrobial classes, respectively.

Conclusions—MDRGN are spread both within and between nursing homes among residents with advanced dementia. Infection control interventions should begin to target this high-risk group of nursing home residents.

Keywords

Multidrug-resistance; gram-negative bacteria; long-term care; advanced dementia; nursing homes; cross-transmission

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Conflict of Interest: All authors report no conflicts to disclose pertinent to this article.

INTRODUCTION

Multidrug-resistant gram-negative bacteria (MDRGN) are associated with considerable morbidity, mortality and excess hospital costs.¹ Limited therapeutic options to treat MDRGN infections and the paucity of novel antimicrobials targeting MDRGN further increase the public health risk posed by these pathogens.¹ In the last decade, it has become evident that nursing home residents are among the major reservoirs of MDRGN with up to 20–40% of residents colonized or infected with MDRGN.^{2,3} Furthermore, frequent hospitalizations among this patient population provide a constant influx of MDRGN into the hospital setting with spread to other patients.⁴

Recent studies have identified residents with advanced dementia as having a three-fold higher risk of harboring MDRGN than other residents in nursing homes.⁵ Residents with advanced dementia have minimal verbal ability, are incontinent of urine and feces and have lost basic motor skills. Thus, their poor functional status and need for increased contact with healthcare workers substantially increases their likelihood of both acquiring and spreading MDRGN. Furthermore, residents with advanced dementia are frequently exposed to antimicrobials, with 66% receiving at least one course of antimicrobials in an 18-month period.⁶

Studies of the molecular epidemiology of multidrug-resistant organisms in nursing home have shown transmission between residents and, contamination of common rooms and healthcare workers as modes of spread.^{7–9} These studies however, did not specifically address residents with advanced dementia. In September 2009, a 5-year cohort study (Study of Pathogen Resistance and Exposure to Antimicrobials in Dementia [SPREAD]) was initiated to quantify the prevalence, acquisition and risk factors for multidrug-resistant organisms.¹⁰ In the SPREAD study, 362 residents with advanced dementia were followed for up to one year. Forty-six percent of residents were colonized with at least one MDRGN species at baseline and 36% acquired at least one MDRGN over the 12-month study period.¹⁰ In the present study, we present the findings of the molecular epidemiology of MDRGN transmission within and between nursing homes and, characterize MDRGN colonization among residents with advanced dementia.

METHODS

Study design

Residents with advanced dementia were recruited as part of the SPREAD study. The detailed methodology of SPREAD has been previously published.¹¹ Briefly, criteria for subject eligibility included 1] ≥ 65 years of age, 2] length of stay in nursing home greater than 30 days, 3] dementia of any type, 4] formally or informally appointed proxy was available and could communicate in English and 5] a Global Deterioration Score (GDS) equal to 7. A GDS of 7 requires very severe cognitive dysfunction, limited verbal ability (<5 words), incontinence of urine and stool and loss of basic motor skills.¹² Resident assessments were performed every three months for up to one year or death. Assessments included the collection of demographic and clinical data, and rectal swabs. Demographic variables included age, gender, race, etiology of dementia and comorbid conditions. The

BANS_S score was used as a measure of functional disability, with a higher score representing increased disability. The Test for severe impairment, another measure of disability, was also documented, with lower scores indicating greater cognitive impairment. Nursing home characteristics were collected using the Centers for Medicare and Medicaid Nursing Home Compare website, provided by Medicare.¹³ These characteristics included number of beds, presence of special care dementia unit and number of healthcare workers hours, by type, per resident per day. Exposure to antimicrobials was classified as appropriate if minimal criteria for the initiation of antimicrobials for a suspected infection were met, as per the modified Society of Healthcare Epidemiology of America guidelines.¹⁴ Only those nursing homes in which MDRGN isolates were recovered from more than one patient and in which at least one acquisition event occurred were included in this study. Acquisition was defined as a negative baseline rectal specimen for MDRGN and at least one positive follow-up specimen.

The Institutional Review Board at Hebrew Senior Life and the Clinical Committee of Investigation at Beth Israel Deaconess Medical Center, approved the conduct of this study.

Microbiological Methods and Molecular Typing

MDRGN were isolated from specimens by plating rectal swabs on McConkey media, supplemented with 2µg of ciprofloxacin/mL or 2µg of ceftazidime/mL to minimize the recovery of pansusceptible gram-negative bacteria. Species identification and susceptibility testing were performed as previously described.¹¹ MDRGN isolates included those from the family *Enterobacteriaceae* and were defined as gram-negative bacteria resistant to three or more of the following antimicrobials or antimicrobial classes: ciprofloxacin, extended-spectrum penicillins (ampicillin/sulbactam or piperacillin/tazobactam), meropenem, gentamicin, third-generation cephalosporins (ceftazidime or ceftriaxone). Molecular typing of MDRGN isolates was performed using pulsed-field gel electrophoresis, as previously described¹¹. Indistinguishable or closely related strains, defined as strains differing by 3 bands were considered clonally-related as per the criteria of Tenover *et al.*¹⁵

RESULTS

Resident and nursing home characteristics

At least one acquisition event occurred in 22 (62.8%) of the 35 enrolled nursing homes in the SPREAD study. Nursing home characteristics for 20 of these 22 nursing homes are shown in Table 1. Two nursing homes closed soon after completion of data collection and therefore characteristics from the Nursing Home Compare website were no longer available. Resident characteristics are presented in Table 2.

MDRGN isolates

A total of 190 MDRGN isolates from 152 residents, residing in 22 nursing homes, were included in the analyses. A total of 28 (18.4%) residents were colonized with more than one different MDRGN species (4 residents were colonized with 3 different MDRGN species and 24 were colonized with 2 different MDRGN species). MDRGN species, recovered by nursing homes, are shown in Table 3. MDR-*E.coli* and MDR-*P.mirabilis* were the most

common species, recovered from 42.6% and 32.6% of residents, respectively. Susceptibility profiles to individual antimicrobials or antimicrobial classes are shown in Table 4. A total of 168 (88.4%), 20 (10.5%) and 2 (1%) of MDRGN were resistant to three, four and five antimicrobials or classes, respectively. The most common 3-drug resistant pattern was resistance to ciprofloxacin, gentamicin, and extended-spectrum penicillins, present among 74.4% (125/168) of isolates, followed by resistance to ciprofloxacin, extended-spectrum penicillins and third-generation cephalosporins, present among 23.2% (39/169) of isolates. All 20 4-drug resistant MDRGN isolates were resistant to ciprofloxacin, extended-spectrum penicillins, third-generation cephalosporins and gentamicin.

Pulsed-field gel electrophoresis typing of MDRGN isolates

Genetically-related MDRGN strains, recovered from different residents, were detected in 18 (82%) of the 22 nursing homes. The percent of clonally-related strains in these nursing homes ranged from 0% to 86% (average 35%). More than 50% of strains were clonally-related in three nursing homes (Table 3). Genetically-related MDRGN strains were also identified in different nursing homes. Three indistinguishable MDR-*P.mirabilis* strains and MDR-*P.stuartii*, each, were recovered from residents residing in three different nursing homes (nursing homes C, D, and F, and nursing homes H, O and S, respectively). Two sets of two indistinguishable strains of MDR-*E.coli* were recovered from nursing homes F and G. Two indistinguishable strains of MDR-*E.coli* were also recovered from nursing homes J and K, and nursing homes I and M. Lastly, two indistinguishable strains of *M.morgannii* were recovered from nursing homes D and R (Figure 1).

DISCUSSION

In this prospective study, we characterized the transmission dynamics of MDRGN among residents with advanced dementia residing in 22 nursing homes. The main findings were 1] cross-transmission of MDRGN was frequently identified both within nursing homes and between nursing homes, 2] antimicrobial resistance to four and five different antimicrobials or antimicrobial classes was present among 11.5% of MDRGN isolates and 3] almost one in five residents were colonized with more than one different MDRGN species.

Transmission of multidrug-resistant organisms within long term care facilities has been well characterized.^{7-9,16,17} In this study, we show that cross-transmission among residents with advanced dementia also contribute to the spread of MDRGN in this healthcare setting. Although these residents, by definition are non-ambulatory, increased requirement for healthcare worker assistance and frequent antimicrobial exposure, leads to a subset of long term care facility residents at high risk of both acquiring and spreading MDRGN. Furthermore, residents with advanced dementia spend numerous hours every day in common rooms during which time they interact with both advanced dementia and non-advanced dementia residents. These interactions could provide opportunities for direct resident-to-resident transmission and environmental contamination. Future studies, aimed at characterizing the transmission dynamics of MDRGN and quantifying the impact of infection control strategies in nursing homes, should include analyses targeted to this high-risk group.

Transmission of clonal MDRGN strains between residents with advanced dementia, residing in multiple different nursing homes, was also documented. Possible routes include overlapping hospital stays among residents with advanced dementia from different nursing homes and healthcare workers cross-covering multiple nursing homes. Several multicenter nursing home studies of multidrug-resistant organisms among all residents, have also implicated that overlapping hospital stays contributes to the inter-facility spread of these organisms.^{9,16,18}

The extent of cross-transmission varied among different nursing homes. The reasons are likely multifactorial and may include varying compliance rates with hand hygiene, number of health care workers and use of antimicrobials. A study by Cochard *et al.* (2014) showed that the prevalence of multidrug-resistant Enterobacteriaceae was associated with lower rates of hand hygiene, use of gloves and protective clothing, as well as lower rates of appropriate waste management.¹⁹ The implementation of multifaceted infection control interventions however, can reduce the spread of multidrug-resistant organisms. A nation-wide intervention to prevent the spread of carbapenem-resistant Enterobacteriaceae in Israel, which included periodic on-site evaluations of infection control policies, development of national guidelines involving active surveillance and contact isolation of colonized residents, and cross-sectional surveys of colonization rates, significantly decreased the rate of carbapenem-resistant Enterobacteriaceae.²⁰

We did not address the extent of MDRGN transmission from residents with advanced dementia to nursing home residents without advanced dementia. It is likely that the former contribute to the acquisition of MDRGN to other residents during overlapping exposure in common rooms, contact with the same healthcare worker and environmental contamination. Some nursing homes provide special care wards for residents with advanced dementia and whether these types of nursing homes have lower rates of transmission to nursing home residents without advanced dementia, requires further investigation.

Another important finding of this study was the substantial number of residents with advanced dementia who were colonized with MDRGN that were resistant not only to three, but to four and five different antimicrobials or antimicrobial classes. The paucity of novel anti-gram negative agents being developed by industry and the current limited therapeutic options to treat residents with MDRGN infections further emphasize the urgent need to limit MDRGN spread.

Lastly, we showed that co-colonization with multiple different MDRGN species was frequent among residents with advanced dementia. A study by Snyder *et al.* also showed that among all residents in nursing homes, 25% were co-colonized with multiple MDRGN species and that markers of advanced dementia were significantly associated with co-colonization.²¹ The high rate of co-colonization has important infection control implications. At present, screening cultures for MDRGN, if performed, target only one type of MDRGN species. However, since residents can be colonized with more than one different MDRGN species, identifying only one MDRGN species may lead to inadequate cohorting of colonized residents.

This study has several limitations. First, the duration of follow-up for each nursing home varied and therefore greater transmission events may have been identified in those nursing homes with a longer duration of follow-up. Second, we did not quantify the contribution of horizontal gene transmission in the acquisition and spread of MDRGN as it was beyond the scope of this study.²² Third, only residents with advanced dementia who participated in this study were screened for MDRGN and other nursing homes residents were not included in this epidemiological investigation. Thus, the full extent of MDRGN transmission within nursing homes was not characterized. Lastly, characteristics of nursing homes, including antimicrobial exposure, were described but differences among nursing homes and their potential association with extent of transmission could not be analyzed due to a small sample size.

The ongoing rise of MDRGN within nursing homes raises serious concerns for improving the clinical outcome of these residents.^{8,23} Only 50% of nursing home residents in whom MDRGN are recovered from clinical cultures during a hospitalization, return to their nursing home, with the remainder requiring higher level of care or dying.²³ Ongoing efforts to curb the acquisition and spread of MDRGN among residents of nursing homes, especially those with advanced dementia, are crucial.

Acknowledgments

The investigators wish to thank the SPREAD data collection and management team (Ruth Carroll, Margaret Bryan, and Elaine Bargmen), all the staff at the participant nursing homes, and the residents and families who have generously given their time to this study.

Financial Support: This work was supported by NIH-NIA R01 AG032982. Dr. Mitchell is supported by NIH-NIA K24AG033640.

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Figure 1.

Percent of clonally-related strains of multidrug-resistant gram-negative bacteria within and between nursing homes among residents with advanced dementia

Table 1

Characteristics of 20 nursing homes* participating in the SPREAD study with 1 multidrug-resistant gram-negative bacteria acquisition event

Nursing Home Characteristic	Value
Average number of beds (range)	149 (48–333)
Special care dementia unit (%)	18 (90)
Medicaid bed (%)	19 (95%)
For profit (%)	12 (60%)
Average licensed staffing hours/resident/day (range)	1.7 (1.3–3.1)
Average certified nursing assistant staffing hours/resident/day (range)	2.4–3.5
Average registered nurse staffing hours/resident/day (range)	1.0 (0.6–2.6)
Average number of health deficiencies over 3 years (range)	8.5 (0–25)
Percent of residents who received at least one course of antimicrobials (range)	31 (0–67)
Percent of residents who received at least one course of appropriate antimicrobials (range)	36 (0–67)
Percent of residents hospitalized at least once (range)	12 (0–44)

* data were unavailable for 2 nursing homes

Table 2

Baseline characteristics of nursing home residents with advanced dementia (N=152)

Resident Characteristic	No. (%) or mean $\pm$ SD
Age (year), mean $\pm$ SD	86.4 $\pm$ 7.3
Female, %	131 (86.2)
White, %	144 (94.7)
Etiology of dementia, % *	
Alzheimer's dementia	105 (69.1)
Vascular dementia	21 (13.8)
Other dementia	29 (19.1)
Comorbid conditions, %	
Congestive heart failure	31 (20.4)
Chronic obstructive pulmonary disease	13 (8.6)
Diabetes mellitus	32 (21.1)
BANS_S score [†] , mean $\pm$ SD	21.4 $\pm$ 2.8
Test for severe impairment = 0,% [‡]	51 (33.6)

* Total exceeds 100% because some residents had more than one type of dementia.

[†] BANS_S=Bedford Alzheimer's Nursing Severity-Subscale, possible range 7–28, higher scores indicate more functional disability

[‡] TSI=Test for Severe Impairment, possible range 0–24, lower scores indicate greater cognitive impairment; dichotomized to equal to 0 vs. > 0.

Table 3

Number of multidrug-resistant strains and species per number of residents for each enrolled nursing home

Nursing Home	Total number of multidrug-resistant strains/number of residents	Number of multidrug-resistant strains/number of isolates				Months in study
		<i>E.coli</i>	<i>P.mirabilis</i>	<i>P.stuartii</i>	<i>M.morganii</i>	<i>K.pneumoniae</i>
Total**	110/190	62/81	32/62	7/29	6/14	4/4
A	2/2	2/2				29
B	4/5	4/5				10
C	1/7		1/7			26
D	14/22	6/10	6/8		2/4	30
E	3/4		2/2	1/2		11
F	23/44	12/16	8/10	3/16		34
G	3/11	2/2	1/9			32
H	3/4	1/2		2/2		12
I	16/17	8/8	4/5		2/2	34
J	4/6	4/6				21
K	2/4	2/4				12
L	2/2	2/2				6
M	3/3	3/3				12
N	7/7	4/4	3/3			15
O	3/5	2/2		1/3		18
P	1/3		1/3			21
Q	8/11	5/5	3/6			27
R	1/2				1/2	<1
S	4/6	3/3		1/3		9
T	9/15	3/3	5/9		1/3	12
U	1/2	1/2				9
V	4/8	2/2		1/3	1/3	12

* Total number of strains is less than if all strains per individual nursing home are added, since some strains were recovered from 2 nursing homes

Antimicrobial susceptibility profiles of multidrug-resistant gram-negative bacteria recovered from 22 nursing homes

Table 4

Multidrug-resistant isolate	Ciprofloxacin (%)	Third/fourth-generation cephalosporins (%)	Extended-spectrum penicillins (%)	Gentamicin (%)	Meropenem (%)
<i>E. coli</i> (N=81)	80 (98.8)	52 (64.2)	80 (98.8)	51 (63.0)	2 (2.5)
<i>P. mirabilis</i> (N=62)	62 (100)	1 (1.6)	61 (98.4)	62 (100)	0 (0)
<i>P. stuartii</i> (N=29)	29 (100)	1 (11.1)	29 (100)	28 (96.6)	0 (0)
<i>M. morganii</i> (N=14)	13 (92.8)	9 (64.3)	14 (100)	7 (50.0)	0 (0)
<i>K. pneumoniae</i> (N=4)	4 (100)	2 (50.0)	4 (100)	3 (75.0)	0 (0)