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Epidemiology of Gram Negative Antimicrobial Resistance in a Multi-State Network of Long Term Care Facilities

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Abstract

We identified 1,805 gram-negative organisms in urine cultures from residents of 63 long-term care facilities (LTCFs) over 10 months. Fluoroquinolone resistance was 51% among *E. coli*, while 26% and 6% of Klebsiella were resistant to ceftazidime and imipenem, respectively. Resistance varied significantly by type of LTCF, LTCF size, and geographic region.

Keywords

Resistance; gram-negative; long-term care

Introduction

Increasing attention has been focused on the importance of antimicrobial resistance in the long-term-care facility (LTCF) population [1-3]. Antimicrobial resistance in this rapidly growing segment of the population is important because these patients often have multiple comorbidities and functional impairments that increase susceptibility to infection [4,5]. Furthermore, LTCF residents are frequently treated empirically with broad-spectrum antibiotics, which increase selection pressure for resistance [6]. Curbing emergence of antibiotic-resistant pathogens in the LTCF has challenges that are unique to this setting including fewer nursing resources, less availability of diagnostic testing, and morbidity associated with isolation control practices [1, 3-5].

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The epidemiology of antimicrobial resistance in LTCFs remains poorly understood. Furthermore, most available data are derived from single centers. How resistance patterns differ across geographic regions, facility type (e.g., skilled nursing, assisted living), and facility bed size has not been well defined. Understanding the impact of these characteristics on resistance patterns would provide important insights to inform strategies to curb future emergence of resistance. The goals of this study were to identify the prevalence of antimicrobial resistance among urine isolates from a network of LTCFs, and to elucidate differences in resistance patterns across geographic regions, facility type, and facility size.

Methods

We conducted a cross sectional study in a network of 63 LTCFs located across three US states (New Jersey, Pennsylvania, and Delaware). All microbiologic analyses of urine cultures for these LTCFs are performed by a single laboratory (Silver Labs Inc., Cherry Hill, NJ). Species identification and antimicrobial susceptibilities were confirmed according to criteria of the Clinical and Laboratory Standards Institute (CLSI) using the Microscan Walkaway (Dade Behring Inc, West Sacramento, CA) automated susceptibility testing system [7]. All urine cultures obtained from January 15, 2008 through November 15, 2008 were included. No repeat isolates from the same patient were included.

Initially, we assessed overall susceptibilities of all gram-negative organisms to the tested antimicrobial agents. These agents were amikacin, amoxicillin/clavulanate, ampicillin/sulbactam, aztreonam, cefazolin, cefepime, ceftazidime, ceftriaxone, gentamicin, imipenem, levofloxacin, piperacillin-tazobactam, tetracycline, tobramycin, and trimethoprim-sulfamethoxazole (TMP-SMX).

Subsequently, we focused on the three most commonly isolated organisms: *Escherichia coli*, *Klebsiella* species, and *Proteus mirabilis*. For these organisms, we assessed differences in the prevalence of resistance by geographic region, institution size, and institution type (i.e., skilled nursing facility (SNF) vs. assisted living facility (ALF)). Geographic location of the LTCF was assigned to one of six pre-determined geographic regions. These regions were based on counties and were divided into the following regions: Northern New Jersey, Central New Jersey, Southern New Jersey, Coastal New Jersey, Southeastern Pennsylvania, and Delaware. LTCFs were grouped into different size categories as follows: 1) <100 beds; 2) 100-150 beds; 3) 151-200 beds; and >200 beds). In analyzing difference across geographic regions and bed size, we focused only on SNFs as the majority of clinical isolates came from SNFs rather than ALFs. Differences in prevalence were assessed using an overall chi-square test [8]. All statistical calculations were performed using STATA version 10.0 (Stata Corp, College Station TX).

Approval was obtained from the Institutional Review Board of the University of Pennsylvania.

Results

Among residents of the 63 included facilities, there were 1,805 gram-negative organisms identified during the study period, including 1,653 isolates from SNF residents and 152 isolates from ALF residents. The three most common gram-negative organisms were E. coli (n=874), Klebsiella species (n=323); and P. mirabilis (n=285). For all organisms, there was substantial resistance to various antibiotics tested. Notably, the prevalence of levofloxacin resistance was 51% among *E. coli* and 29% for *Klebsiella* species. The prevalence of ceftazidime resistance (often used as a marker for extended-spectrum beta-lactamase (ESBL)-mediated resistance) was 26% among *Klebsiella* species and 12% among *E. coli*. Finally, 6% of *Klebsiella* species and 37% of *Pseudomonas aeruginosa* were resistant to imipenem.

Among the 63 included facilities, there were 44 skilled nursing facilities (SNFs) and 19 assisted living facilities (ALFs). There were many significant differences in antimicrobial susceptibilities when comparing ALFs and SNFs (Table 1).

Among the 44 SNFs, 12 facilities had <100 beds, 12 had 101-150 beds, 13 had 151-200 beds, and seven facilities had >200 beds. Among *E. coli*, there were significant differences in susceptibilities to the following agents (for bed sizes <100, 100-150, 151-200, and >200, respectively): aztreonam (79%, 90%, 87%, and 87%; p=0.005); cefepime (84%, 92%, 88%, and 88%; p=0.03); ceftazidime (81%, 92%, 88%, and 87%; p=0.003); and ceftriaxone (79%, 92%, 87%, and 87%; p=0.001). Among *Klebsiella*, there were no significant differences in susceptibilities across facilities of different sizes. Finally, among *P. mirabilis*, there were significant differences in susceptibilities to the following agents (for bed sizes <100, 100-150, 151-200, and >200, respectively): ampicillin-sulbactam (74%, 89%, 87%, and 92%; p=0.02); and cefazolin (74%, 91%, 88%, and 92%; p=0.02). Of note, the distribution of SNFs within a geographic region with regard to bed size was not substantively different across geographic regions.

The 44 SNFs represented six different geographic regions. The number of SNFs in each region ranged from four to 16 (median = 6.0) and the distribution by facility type and size were similar across the six regions. There were significant differences in antimicrobial susceptibilities across geographic regions (Table 2).

Discussion

Among a broad range of gram-negative organisms, there is was marked resistance to multiple antibiotics. Furthermore, resistance rates varied significantly by type of facility (i.e., SNF vs. ALF), LTCF size, and geographic region. This variability in resistance may be due to various differences across facilities including patient populations, antimicrobial use patterns and infection control practices. To elucidate the reasons for the variability in prevalence of resistance, studies specifically examining institutional and individual level risk factors for resistance should be pursued. Furthermore, given the marked differences across facilities, future studies should include multiple facilities to improve the generalizability of the results.

The high levels of resistance noted in this study have important implications for future therapeutic options. Fluoroquinolones are very commonly used in the LTCF setting but the very high rates of resistance will limit their future use. The prevalence of ceftazidime resistance (often used as a marker for ESBL-producing organisms) was also noted to be very high. Future studies should more clearly elucidate the epidemiology of ESBL-mediated resistance specifically in the LTCF setting [9]. Finally, we noted imipenem resistance among Klebsiella (~6%) which was greatest in the Northern New Jersey geographic region. Given recent increases in carbapenemase-producing Klebsiella noted in particular in the New York City region, trends in carbapenem resistance in LTCF patients must be monitored very closely [10].

There are several potential limitations to our study. First, we were unable to determine whether isolates represented infection versus colonization. Second, LTCFs might choose to transfer a patient with suspected infection to an acute care facility without obtaining cultures. As such patients would likely be at increased risk of a resistant infection, the result of such a practice would be to underestimate the prevalence of resistance.

We found marked resistance to multiple antibiotics among urine cultures from LTCF residents. Furthermore, resistance rates varied significantly by type of facility, facility size, and geographic region. These results show the continued decrease in antibiotic therapy options in

LTCF residents and emphasize the critical need for rigorous, multi-facility, research focused on elucidating the epidemiology of resistance in the LTCF population.

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Table 1

Antimicrobial Susceptibilities by Type of Facility

Organisms	Facilities	Test	AMK	A/C	AZT	CFZ	CPM	CTZ	CAX	LVX	P/T	TOB	T/S
E. Coli	ALF=19	68	100	84	91	82	96	94	94	66	96	84	75
	SNF-44	806	99	76	87	76	89	88	87	47	95	79	62
	P value		*NS*	*0.09*	*NS*	*0.14*	*0.06*	*0.08*	*0.06*	*0.002*	*NS*	*NS*	*0.02*
Klebsiella spp	ALF=19	30	93	93	93	90	90	90	90	93	93	93	93
	SNF-44	293	79	78	71	69	73	72	72	69	75	71	68
	P value		*0.04*	*0.03*	*0.004*	*0.009*	*0.03*	*0.02*	*0.02*	*0.002*	*0.01*	*0.004*	*0.002*
P. Mirabilis	ALF=19	19	95	100	95	89	95	95	95	68	100	89	84
	SNF-44	266	100	94	97	87	98	97	97	52	100	92	77
	P value		*NS*	*NS*	*NS*	*NS*	*NS*	*NS*	*NS*	*0.12*	*NS*	*NS*	*NS*

AMK: amikacin; A/C: amoxicillin/clavulanate; AZT: aztreonam; CFZ: cefazolin; CPM: cefepime; CTZ: ceftazidime; CAX: ceftriaxone; LVX: levofloxacin; P/T: piperacillin/tazobactam; TOB: tobramycin; T/S Trimethoprim-sulfamethoxazole

Only those p values ≤0.10 shown

Only those antibiotics shown for which at least one organism was statistically different when comparing SNF and ALFs

Table 2

Antimicrobial Susceptibilities by Region

Organisms	Region-# Sites	TEST	A/C	AZT	CFZ	CPM	CTZ	CAX	GEN	IMP	LVX	P/T	TET	TOB	T/S
E. Coli	All SNF-44	806	76	87	76	89	88	87	82	99	47	95	64	79	62
	North NJ-7	172	79	90	80	91	89	88	80	100	45	94	61	76	60
	Central NJ-6	71	87	94	90	94	94	93	86	100	65	94	75	85	75
	South NJ-16	304	73	85	72	87	85	85	84	100	50	96	64	83	65
	Shore NJ-5	113	77	94	81	96	95	95	74	99	39	96	62	70	58
	DE-4	65	78	86	80	89	89	89	85	100	42	92	60	85	54
	PA-6	81	69	74	63	77	77	75	86	99	40	96	68	80	58
	P value		*0.01*	*<.001*	*<.001*	*0.003*	*<.001*	*<.001*	*0.03*	*NS*	*<.001*	*NS*	*0.08*	*0.03*	*0.01*
Klebsiella spp	All SNF-44	293	78	71	69	73	72	72	86	94	69	75	84	71	68
	North NJ-7	71	69	69	65	70	69	69	85	87	63	70	85	69	65
	Central NJ-6	26	58	54	54	58	54	54	69	85	58	50	69	54	50
	South NJ-16	110	84	75	75	78	76	76	86	98	75	81	85	78	75
	Shore NJ-5	29	86	86	83	86	86	86	93	97	86	86	83	90	83
	DE-4	29	97	62	62	62	62	62	97	100	59	83	90	59	59
	PA-6	28	71	71	64	71	71	71	82	89	64	71	89	57	61
	P value		*0.01*	*0.07*	*0.04*	*0.04*	*0.07*	*0.07*	*0.009*	*0.04*	*0.04*	*0.008*	*0.09*	*0.005*	*0.02*
P. Mirabilis	All SNF-44	266	94	97	87	98	97	97	88	100	52	100	0	92	77
	North NJ-7	51	96	100	94	100	100	100	98	100	51	100	0	100	84
	Central NJ-6	37	95	95	84	97	97	95	97	100	43	100	0	95	95
	South NJ-16	94	93	97	86	99	98	99	80	100	51	100	0	88	72
	Shore NJ-5	25	100	96	88	96	96	96	80	100	52	100	0	80	76
	DE-4	26	96	96	92	96	96	96	96	100	69	100	0	96	73
	PA-6	34	91	94	79	94	91	94	85	100	53	100	0	94	65
	P value		*NS*	*NS*	*0.08*	*NS*	*0.06*	*NS*	*0.002*	*NS*	*0.07*	*NS*	*NS*	*0.003*	*0.002*

AMK: amikacin; A/C: amoxicillin/clavulanate; AZT: aztreonam; CFZ: cefazolin; CPM: cefepime; CTZ: ceftazidime; CAX: ceftriaxone; GEN: gentamicin; IMP: imipenem; LVX: levofloxacin; P/T: piperacillin/tazobactam; TET: tetracycline; TOB: tobramycin; T/S Trimethoprim-sulfamethoxazole

Only those p values ≤0.10 shown

Only those antibiotics shown for which at least one organism was statistically different when comparing SNF and ALFs