

The Emerging Threat of Multidrug-Resistant Gram-Negative Organisms in Long-Term Care Facilities

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Background. Infections caused by antimicrobial-resistant bacteria are associated with substantial morbidity and mortality. Residents of long-term care facilities (LTCF) are among the main reservoirs of antimicrobial-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Multidrug-resistant gram-negative organisms (MDRGN) are emerging as important pathogens among LTCF residents. Data on the clinical epidemiology of MDRGN, especially in comparison to VRE and MRSA, are limited.

Methods. All clinical cultures collected from residents of a 750-bed LTCF for a period of 2 years were analyzed for the presence of MDRGN, VRE, and MRSA. Multidrug resistance among gram-negative bacteria was defined as resistance to three or more antimicrobials or antimicrobial groups including extended-spectrum penicillins (ampicillin/sulbactam or piperacillin/tazobactam), cephalosporins (cefazolin or ceftriaxone), gentamicin, ciprofloxacin, and trimethoprim-sulfamethoxazole (TMP/SMX).

Results. A total of 1,661 clinical cultures were included in the analysis. MDRGN were recovered from 180 (10.8%) cultures, MRSA from 104 (6.3%), and VRE from 11 (0.6%). MDRGN were isolated more frequently than MRSA or VRE throughout the study period. The prevalence of MDRGN increased significantly from 7% in 2003 to 13% in 2005 ($p = .001$). More than 80% of MDRGN isolates were resistant to ciprofloxacin, TMP/SMX, and ampicillin/sulbactam. Resistance to three, four, and five or more antimicrobials were identified among 122 (67.8%), 47 (26.1%), and 11 (6.1%) MDRGN isolates, respectively.

Conclusions. Rates of MDRGN exceeded those of MRSA and VRE and increased throughout the study period. Resistance to multiple, commonly prescribed antimicrobials among MDRGN raises concerns about therapeutic options available to treat MDRGN infections among LTCF residents.

Key Words: Antimicrobial resistance—Long-term care—Multidrug-resistant gram negative—Geriatrics.

THE rapid and ongoing spread of antimicrobial-resistant bacteria throughout all health care institutions is considered a critical medical and public health issue (1). Residents of long-term care facilities (LTCF) are one of the main reservoirs of antimicrobial-resistant bacteria with reported prevalence rates similar to patients in the intensive care unit (2–6). Epidemiological studies and infection control initiatives in LTCF have focused predominantly on methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Recently, it has become apparent that multidrug resistance among gram-negative bacteria is becoming an even greater problem in these facilities, with more than half of LTCF residents harboring multidrug-resistant gram-negative bacteria (MDRGN) (5). Infections caused by MDRGN are associated with higher mortality rates, longer length of hospital stays, and greater hospital costs compared with infections caused by antimicrobial-susceptible gram-negative bacteria (7). Health care costs associated with MDRGN infections are even greater than those associated with MRSA infections (8). Despite the poor outcomes associated with MDRGN infections, few studies have focused on these emerging antimicrobial-resistant bacteria in the LTCF population and compared its relevance to other more frequently studied antimicrobial-resistant bacteria, including MRSA and VRE.

The goal of this study was to provide detailed data on the prevalence and temporal trends of MDRGN, MRSA, and VRE from one large urban LTCF for a period of 2 years. These data are needed to further our understanding of the transmission dynamics of antimicrobial-resistant bacteria within the LTCF setting and ultimately design effective and appropriate infection control strategies aimed at limiting the spread of antimicrobial-resistant bacteria, not only in our elderly population but also to other patient populations they encounter in the acute care and community settings.

METHODS

The study was performed at the Hebrew Rehabilitation Center for the Aged, which provides care for an average of 700 LTC residents and 50 acute rehabilitation residents in the metropolitan Boston, Massachusetts, area. Microbiology records of all clinical cultures (collected as a part of routine medical care), obtained from residents between November 2003 and September 2005, were reviewed retrospectively. All cultures were processed at a single off-site commercial microbiology laboratory. Demographic information for the study population was obtained by extracting existing data from the Minimum Data Set (MDS). The MDS

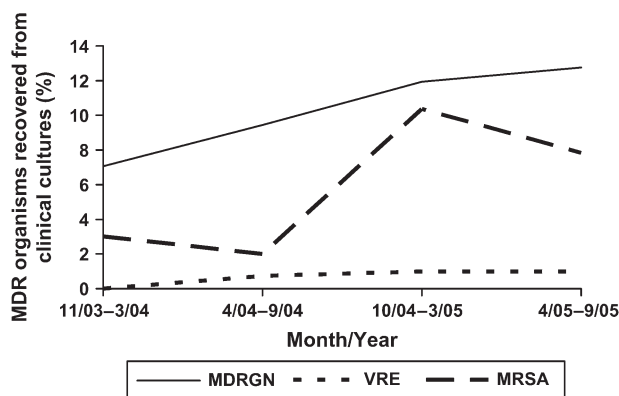


Figure 1. Rates of Multidrug-Resistant Gram-Negative Bacteria (MDRGN), Vancomycin-Resistant Enterococci (VRE), and Methicillin-Resistant *Staphylococcus aureus* (MRSA) Recovered From Clinical Cultures for the Study Period.

is a core set of items and includes demographic information and clinical indicators used to assess all of the nation's nursing home residents who reside in facilities participating in the Medicare or Medicaid programs. Data extracted from MDS have been widely used and demonstrated to be reliable for research purposes (9,10). Demographic data in the form of age, gender, and length of stay were obtained in aggregate form via an MDS query using SPSS (SPSS Inc., Chicago, IL) for extraction and analysis. The most recent full MDS assessment conducted on each resident during the study period was used for analysis.

Clinical cultures positive for MDRGN, MRSA, and VRE were included in the analysis. Antibiotics chosen for inclusion in the definition of multidrug resistance among gram-negative bacteria included those in which susceptibility testing was reported for at least 80% of isolates per study year. Criteria for multidrug resistance among gram-negative bacteria were defined as resistance or intermediate resistance to three or more of the following antimicrobials or antimicrobial groups consistent with previously published work (5,6): extended-spectrum penicillins (ampicillin/sulbactam or piperacillin/tazobactam), cephalosporins (cefazolin or ceftriaxone), gentamicin, ciprofloxacin, and trimethoprim-sulfamethoxazole (TMP/SMX).

The prevalence of MDR bacteria, coresistance patterns among MDRGN, and temporal trends over time were analyzed. The study period was divided into four time intervals to reduce monthly fluctuations. Only one isolate per resident per month was included for those residents in whom multiple MDR bacteria with identical susceptibility patterns were recovered from multiple cultures. Temporal trends in antimicrobial resistance were analyzed using the chi-squared test for trend. p values of <0.5 were considered statistically significant. All analyses were performed using STATA 10.0 (Stata Corp., College Station, TX). The conduct of this study was approved by the institutional review board at the study institution.

RESULTS

A total of 975 residents resided in the LTCF during the study period. The average age for this population was 88.2 years (standard deviation ± 7.9) of whom 74.6% were women. Caucasians represented 98.5% of the study population, with other racial groups, including Native American, Black, and Hispanic, accounting for less than 1% each. A total of 313 (32.1%) residents died during the study period. A total of 3,578 clinical cultures were obtained during the study period, of which 3,029 (84.7%) were from urine, 307 (8.6%) from blood, and 242 (6.8%) from wound specimens. Bacterial growth was identified among 2,032 (56.8%) cultures, of which 1,789 (88%), 224 (11%), and 19 (1.0%) were recovered from urine, wound, and blood specimens, respectively. Cultures reported as normal flora, mixed growth, or probable contaminant (355 [17.5%]), and repeat cultures growing the same organisms with identical susceptibility patterns, taken from a single individual within a 1-month period (16 [0.007%]), were excluded. The remaining 1,661 isolates are described in the following analysis.

A total of 824 (49.6%) isolates were identified as gram-negative bacteria, of which 180 (21.8%) met the criteria defined in this study for multidrug resistance. Gram-positive bacteria were isolated from 837 cultures of which 104 (12.4%) isolates were identified as MRSA and 11 (1.3%) isolates were identified as VRE. MRSA was recovered from urine (56.7%) and wound (43.3%) cultures. VRE was recovered from urine (90.9%) and wound (9.1%) cultures. Rates of VRE, MRSA, and MDRGN during the study period are shown in Figure 1. For the 6-month intervals during the study period, rates of MDRGN were 7.9%, 9.8%, 13.7%, and 14.0%. MRSA rates were 3.0%, 2.0%, 10.4%, and 7.8%, and rates of VRE were 0.0%, 0.7%, 1.0%, and 1.0%. MDRGN were more frequently isolated than MRSA or VRE throughout the study period. The prevalence of MRSA and MDRGN increased significantly over time ($p = 0.001$ and $p = 0.02$, respectively). MDRGN were recovered from the following sites (number of specimens [percent]): urine (169 [93.9%]), wound (10 [5.6%]), and blood (1 [0.5%]). The most common MDRGN species were *Proteus mirabilis* (92 [51.1%] isolates), *Escherichia coli* (47 [26.1%] isolates), and *Providencia stuartii* (19 [10.6%] isolates). Other species of MDRGN included *Klebsiella pneumoniae* (8 [4.4%] isolates), *Morganella morganii* (5 [2.8%] isolates), *Klebsiella oxytoca* (3 [1.7%] isolates), *Stenotrophomonas maltophilia* (2 [1.1%] isolates), and *Enterobacter aerogenes* (1 [0.6%] isolate). MDRGN isolates were resistant to (percent of isolates) ciprofloxacin (96.7%), ampicillin/sulbactam (92.1%), TMP/SMX (81.5%), gentamicin (79.4%), cefazolin (54.3%), ceftriaxone (13.6%), and piperacillin/tazobactam (5.1%). Susceptibility testing to ceftazidime, cefepime, and imipenem was performed on less than 20% of isolates. A total of 13 different coresistance patterns among MDRGN isolates were identified. Among these, resistance to three, four, and five or more antimicrobials were identified among 122

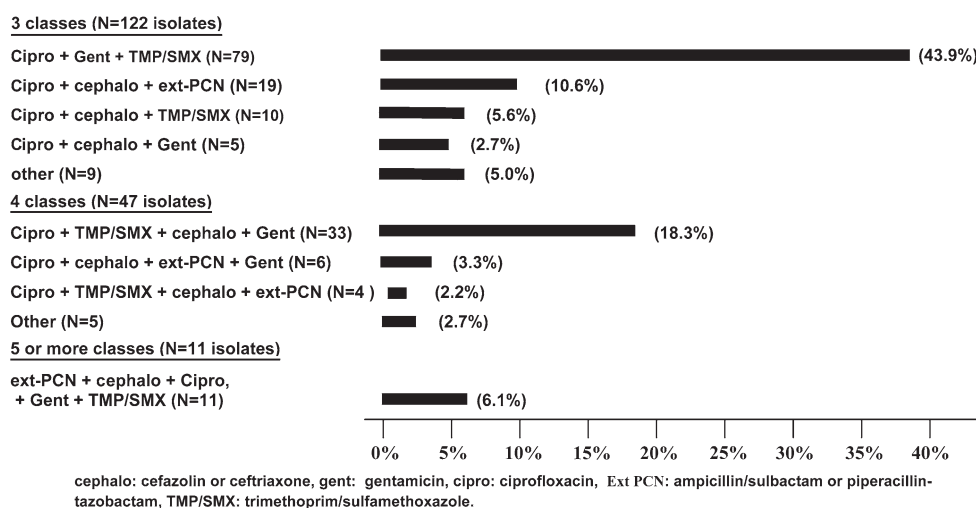


Figure 2. Coresistance patterns among gram-negative bacteria recovered from clinical cultures.

(67.8%), 47 (26.1%), and 11 (6.1%) MDRGN isolates, respectively. The most common coresistant pattern was three-drug resistance to ciprofloxacin, gentamicin, and TMP/SMX present among 79 (43.9%) MDRGN isolates (Figure 2). Coresistance patterns among the most common MDRGN species, *P. mirabilis*, *E. coli*, and *P. stuartii*, were also analyzed. Among *P. mirabilis* isolates, the most common coresistance pattern was three-drug resistance to ciprofloxacin, TMP/SMX, and gentamicin present among 50 (61%) of 82 isolates and a four-drug resistance to ciprofloxacin, TMP/SMX, gentamicin, and cefazolin present among 37 (45%) isolates. The most common coresistance pattern among *E. coli* isolates was also ciprofloxacin, TMP/SMX, and gentamicin present among 30 (64%) of 47 isolates. Among *P. stuartii* isolates, the most common MDR pattern was four-drug resistance to extended-spectrum penicillins, ciprofloxacin, gentamicin, and cefazolin present among 9 (47%) of 19 isolates, and three-drug resistance to extended-spectrum penicillins, cefazolin, and ciprofloxacin present among 8 (42%) isolates.

DISCUSSION

Although VRE and MRSA have been the antimicrobial-resistant bacteria of greatest concern in the LTCF, this study underscores the emerging threat of MDRGN in this patient population. Throughout the 2-year study period, the prevalence of MDRGN surpassed that of MRSA and VRE. Of further concern was the documentation of a steady rise in MDRGN isolates throughout the study period, increasing from 7% in 2003 to 13% in 2005. More than 80% of MDRGN isolates were resistant to commonly prescribed antimicrobials, including ciprofloxacin, TMP/SMX, and ampicillin/sulbactam. Antimicrobial resistance to broader spectrum antimicrobials, although less frequent, was still notable with 14% and 5% of MDRGN isolates resistant to ceftriaxone and piperacillin/tazobactam, respectively. The

majority of MDRGN isolates were resistant to three different antimicrobial groups; however, more than one third were resistant to four or more different antimicrobial groups. These findings raise serious concern about the therapeutic options available to physicians in treating LTCF residents with MDRGN infections. Furthermore, they imply that current infection control efforts focusing on preventing the ongoing rise in VRE and MRSA may need reevaluation to include MDRGN (11). Previous point prevalence studies focusing on the LTCF population have also documented similar rates of multidrug resistance among gram-negative bacteria (12). Risk factors for harboring MDRGN among this patient population include pressure ulcers, poor functional status, advanced dementia, and antimicrobial exposure (12–17). A large prospective study focusing on antimicrobial exposure among residents with advanced dementia documented extensive antimicrobial use in this patient population, with 42% of residents in LTCF receiving antimicrobials within 2 weeks prior to death (13).

The majority of MDRGN isolates were recovered from urine specimens and therefore may have represented colonization as opposed to true infection. Although this finding could imply that there may not be substantial morbidity or mortality associated with the high prevalence of MDRGN in this study, it is important to note that several studies have shown that colonization precedes infection and that 15%–25% of patients colonized with MDRGN will subsequently develop an infection with the identical MDRGN colonizing strain (18,19). Future studies will need to specifically address the outcome of LTCF residents harboring MDRGN.

There are several limitations in this study. First, only pathogens recovered from clinical cultures were included in the analysis, and therefore, residents with asymptomatic colonization may not have been captured. Thus, the prevalence of MDR organisms may be an underestimate. Second, this study was performed at one large urban LTCF and therefore may

not be generalizable to other LTCF. Although the demographics of our patient population is comparable with national averages for other LTCF, differences in health care worker staffing and compliance with infection control measures, in addition to antimicrobial use, may lead to different rates of MDRGN in other LTCF (20,21). Third, there is no standardized definition for multidrug resistance among gram-negative bacteria (22). Nevertheless, the definition used in this study is comparable with previously published definitions (5,6). Lastly, although this study was retrospective in design, the use of computerized microbiological and medical records for data collection minimized any potential biases or omissions.

The novel findings provided from this study emphasize the urgent need for further research on the epidemiology of MDRGN in the LTCF setting, including transmission patterns, the natural history of MDRGN colonization, rates of infection, and associated morbidity and mortality. Hospitals have recently begun to include MDRGN in their surveillance of antimicrobial-resistant bacteria and many have extended the requirement for contact precautions to MDRGN, in addition to VRE and MRSA (23). Future research will determine if similar changes should be implemented in the LTCF setting.

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