Multidrug-Resistant Gram-Negative Organisms and Setting of Onset in Persons with Spinal Cord Injury and Disorder

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Abstract

Background: The number of infections caused by multidrug-resistant gram-negative organisms (MDRGNOs) continues to rise. Individuals with spinal cord injury or disorder (SCI/D) are at an increased risk of infections due to high healthcare utilization and prevalence of comorbidities. While a relationship between MDRGNOs and the SCI/D population had been established, the epidemiologic location of onset had not yet been studied. The goal of this study was to classify and compare characteristics and outcomes related to the epidemiologic location of onset, including hospital-acquired, healthcare-associated, and community-acquired infections of MDRGNOs in veterans with SCI/D.

Methods: A 2-year retrospective cohort study was done of 19,567 patients with SCI/D who received care at a VA facility from 2012-2013. Cultures that were positive for urinary tract, bloodstream, or respiratory infections and received antibiotic use ±7 days were included in the analysis. A total of 2,547 hospital-acquired, 1,989 healthcare-associated, and 1,209 community onset MDRGNO cultures were included in the analysis from 2,607 participants. Bivariate and multivariable, multinomial logistic regression were used to compare the three onset groups with a significance level of $p<0.0167$ due to multiple comparisons.

Results: Compared to the hospital-acquired onset group, healthcare-associated infections had significantly reduced odds of several medical characteristics and comorbidities with pressure ulcers producing the lowest odds of healthcare-associated infection (OR=0.13, 95% CI 0.11-0.15, $p<0.0001$). Hospital-acquired infections compared to community-acquired onset resulted in over a 3-fold greater event frequency for long-term care stay, mechanical ventilation, and surgery (OR=4.53, 95% CI 2.76-7.42, $p<0.0001$, OR=3.53, 95% CI 2.34-5.33, $p<0.0001$, and OR=3.34, 95% CI 2.47-4.51, $p<0.0001$, respectively). Escherichia coli was identified as a causative agent in

52.9% of community-acquired cultures and was found significantly more often in community acquired infections than in hospital-acquired infections ($p<0.0001$). An increased odds of mortality was associated with hospital-acquired infections compared to the community-acquired group for both 90-day and 1-year mortality (OR=2.11, 95% CI 1.41, 3.15, $p=0.0003$ and OR=2.37, 95% CI 1.79-3.14, $p<0.0001$), and healthcare-associated infections were associated with reduced odds of 30-day, 90-day, and 1-year mortality compared to hospital-acquired infections.

Conclusion: Hospital-acquired, healthcare-associated, and community-acquired infections vary by many demographic and medical characteristics, concurrent comorbidities, and causative organisms. Healthcare providers should stay cognizant of the frequency of MDRGNOs when treating individuals with SCI/D due to the high prevalence. Targeted therapies and prevention strategies may be necessary to combat the escalating burden MDRGNOs have on providers, patients, and the entire healthcare system.

Keywords: multidrug-resistance, onset, hospital-acquired, healthcare-associated, community-acquired

Word count: 7,707

Background

In the United States, approximately 285,000 persons are living with a spinal cord injury or disorder (SCI/D), with approximately 17,500 cases added annually as a result of vehicular accidents, violence, falls, and a variety of other onsets.(1) Individuals living with SCI/D utilize health services more frequently than the general population due to high rates of secondary health conditions, such as respiratory diseases, pressure ulcers, sleep disorders, urinary tract infections, chronic pain, and several others.(2,3,4) While many secondary health conditions are often preventable and work has been done to diminish the prevalence in individuals with spinal cord injuries, it is estimated that 20% of the spinal cord population still struggles regularly with at least one secondary health condition.(5)

The large number of secondary health conditions and use of invasive medical devices cause an increased number of infections in persons with SCI/D, particularly urinary tract, respiratory, and bloodstream infections.(6,7,8,9) As a result of increased infections and poor outcomes, persons with SCI/D often use antibiotics as a course of treatment.(10) While antibiotic treatment is often warranted, especially for urinary tract infections, overprescribing often occurs with broad-spectrum antibiotics, especially when physicians are not well versed in caring for individuals with SCIs.(11) For example, patients with SCI/D may be unnecessarily prescribed antibiotics due to a positive culture on medical equipment, which is not a true infection.(12) Consequently, it has been the recommendation that only patients experiencing symptoms should receive antibiotic treatment.(12) Additionally, patients with SCI are often prescribed antibiotics for viral respiratory conditions, even though the antibiotics will not improve the conditions of the patients.(13)

Partially due to the overprescribing of antibiotics, the number of infections caused by multidrug-resistant gram-negative organisms (MDRGNOs) continues to rise annually.(14) Multidrug-resistance has been defined as bacteria that is resistant to at least one antibiotic agent in three different antimicrobial classes.(15) While some antimicrobial resistance is expected naturally over the course of time, the rates currently seen in the world are growing quickly and are largely attributed to antibiotic overuse and misuse.(16) Gram-negative bacteria has been gaining particular attention in the medical community due to the threats posed by antibiotic resistance. The most common gram-negative bacteria in healthcare for patients with SCI/D include *Escherichia coli, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae*.(17)

Gram-negative bacteria differ from gram-positive bacteria in terms of cell structure. While gram-negative bacteria contain an outer-membrane that acts as a permeability barrier, gram-positive are lacking this outside layer.(18) As a result of having an outer barrier, gram-negative bacteria have the intrinsic ability to resist drugs and antibiotics, and the bacteria can then pass genetic materials from its cells to cause further drug resistance in other bacteria as well.(19) In addition to the innate structure of gram-negative bacteria to form resistance, drug resistance can also be acquired by bacteria. Within the DNA of the bacteria, mutations can occur that cause antibiotics to be an ineffective source of treatment. Consequently, mutated strains of bacteria can proliferate and ensure the survival of the strains.(18)

Many strains of bacteria are now partially or fully resistant to available treatments, which is causing excessive illness and healthcare costs in the United States. As of 2013, the CDC found that more than 2 million illnesses and 23,000 deaths were attributable to antimicrobial resistance in the United States.(20) In addition, antibiotic resistance contributes to a large financial cost on the healthcare system; costs are higher for MDR infections than non-MDR infections due to additional tests, more intensive care, longer duration of illness, and more expensive medications required.(16) According to 2000 data, the cost of care for each patient's hospital stay associated with an antibiotic resistant infection ranges from $18,588 to $29,069.(21) Annually, the costs to the U.S. healthcare system as a whole approach $20 million.(22)

Research on MDRGNOs in individuals with SCI/D has been historically difficult due to the changing trends seen in healthcare, such as varying definitions of MDR infections. Furthermore, the majority of older research focused primarily on acute care settings.(23) Since patients with SCI are in contact with a larger continuum of care than the acute care setting, past research likely does not accurately portray trends in this population. However, current research done on persons with SCI estimates that 2 of 5 gram-negative cultures and greater than one third of gram-negative isolates had a MDRGNO, which suggests a high burden within this population.(24)

Moreover, it is important to consider the epidemiologic location of onset of infections to determine where the infection occurred (in the hospital, community, long-term care center, etc). As a result of attaining this information, trends and potential risk factors can be identified. If clear associations are found, the results may influence existing protocols or indicate that completely new standards should be developed. The importance of onset identification has been shown in infections such as pneumonia and bloodstream infections. Pneumonia evidence has shown that individuals with community-acquired infections (CAIs) experience fewer hospitalizations, shorter length of stay and lower mortality than individuals with healthcare-associated infections.(25,26)

While the burden MDRGNOs have on persons with SCI/D has been established, little is known about risk factors for MDRGNOs based on the epidemiologic or patient care setting. In particular, there is no evidence of morbidity and mortality based on epidemiologic location of onset of MDRGNOs in persons with SCI/D. Understanding the variation between hospital-acquired infections, healthcare-associated infections, and community-acquired infections as epidemiologic locations of onset within the SCI/D population may help agencies in the quest to decrease the burden MDRGNOs presently have on morbidity and mortality in the United States.(27)

Of the 250,000 individuals living with SCIs, nearly 42,000 are eligible to receive care at one of the Veterans Affairs (VA) institutions.(28) Across the United States, the VA runs 24 centers specifically devoted to spinal cord injuries and disorders where individuals can receive annual exams and pertinent care for secondary health conditions and other disorders. As the largest provider for persons with SCI/D, the Department of Veteran Affairs (VA) is an exceptional resource for assessing epidemiologic location of onset of MDRGNOs in SCI/D. Therefore, the goal of this study is to classify and compare demographic characteristics, medical characteristics, and mortality outcomes associated with MDRGNO infections based on epidemiologic location of onset in veterans with SCI/D.

Methods

Study Design

A retrospective cohort of microbiology culture data and antibiotic sensitivities was conducted over a 2-year period (1 January 2012 to 31 December 2013) on adult patients with SCI/D. Information on 19,642 patients with SCI/D receiving care in the VA system was available for analysis.

Data Collection

The data used was comprised of clinical patient registries maintained at 142 VA facilities nationwide. Several VA data sources were used within this study, including the VA Spinal Cord Dysfunction (SCD) Registry and Spinal Cord Injury and Disorders Outcomes (SCIDO) databases which are two of the largest and most comprehensive existing databases. To create these databases, clinical registries for patients with SCI/D from individual VA locations were combined to create a single database showing the national scope of SCI/Ds in veterans.

The VA Corporate Data Warehouse (CDW) was used to identify demographic information (age, gender, and race) as well as the clinical setting at the time of culture (inpatient, long-term care, patient clinic/emergency, or home care). The CDW also contains information on comorbidity diagnoses in the past year (to develop Charlson comorbidity score), past healthcare exposure (long-term care stay, inpatient stay) and medical resource utilization. Geographic location based on U.S. Census region and facility characteristics (specialty SCI center or not) provide pertinent information for studying trends in SCI/D. Unless otherwise noted, all relevant exposures or independent variables were evaluated 90 days prior to culture date.

Definitions for MDRGNOs infections

For this study, MDR was defined as any gram-negative organism that is resistant or has intermediate susceptibility to 1 or more antibiotics in at least 3 of the antimicrobial classes. All gram-negative isolates were defined as MDR or non-MDR based on definitions provided by an expert panel comprising the US and European CDC and other partners.(29) Cultures that did not grow at least 1 gram-negative organism and repeat cultures of patients (with a previously positive culture) within 30 days were excluded. Positive cultures were categorized into hospital-acquired, healthcare-associated, or community-acquired based on the CDC criteria established below.

Definitions for Epidemiologic Location of Onset of Infection

Per the CDC, infections that become evident after 48 hours of care and those infections related to receiving treatment for medical or surgical conditions are considered hospital-acquired infections.(30) Contrarily, infections discovered at the time of admission or within 48 hours of admission to the hospital are considered community-acquired infections (CAIs). A third category, healthcare-associated infections, refers to those positive cultures that fit the criteria of CAIs, but also fit the following criteria: *(1)* resided in nursing home or long-term care facility *(2)* within 30 days of positive culture received intravenous therapy at home, wound care, or specialized nursing care through a healthcare agency *(3)* received intravenous chemotherapy or attended a hemodialysis clinic within 30 days of positive culture *(4)* was hospitalized in an acute care hospital for 2 or more days in the 90 days prior to the positive culture.(31) The third category was added as this level was available within the VA databases and emerging evidence details the importance of the healthcare-associated infection category.(31)

Definitions for "True" Infection

For this study, the positive MDRGNO cultures were narrowed down to assist in identifying 'true' infections. For bloodstream infections, infection was defined as a positive blood microbiology culture and incident antibiotic use (±7 days). For urinary tract infections, infection was defined as a positive urine microbiology culture, incident antibiotic use (± 7 days), with the eligible antibiotics being narrowed down to those antibiotics that could be used to treat a urinary tract infection by the expertise of Drs. Katie Suda and Margaret Fitzpatrick at the Edward Hines VA. This was done in an attempt to reduce false positives and eliminate antibiotic use for other, concurrent infections. For respiratory infections, infection was identified by a positive sputum microbiology culture and incident antibiotic use (± 7 days). Once again, the antibiotic list was narrowed to those antibiotics that could be used to treat a respiratory infection. A full list of antibiotics used for urinary tract and respiratory infections is available in **Appendix A.**

Study Population

The database contained information on 27,904 cultures over the two-year span. Of those cultures, 24,170 were identified as urine cultures, 533 were blood cultures, and 987 were sputum cultures (2214 eliminated for being listed as 'other'). Next, "true infection" was identified using the criteria specified earlier of positive culture and incident antibiotic use (± 7 days). After excluding 13,458 cultures that did not meet the specified criteria or used antibiotics not found in **Appendix A**, the dataset was left with 10,883 positive urine cultures, 530 blood cultures, and 819 respiratory cultures. Of the remaining cultures, 5,122 urine cultures, 222 blood cultures, and 401 respiratory cultures were flagged as MDR, bringing the total N for analysis to 5,747. The breakdown for onset is as follows: 2,547 hospital-acquired, 1,989 healthcare-associated, and 1,209 community onset. **Figure 1** details how the final dataset was obtained.

Statistical Analyses

Logistic regression was employed to investigate the associations between hospital-acquired, healthcare-associated, and community-acquired infections. The data for demographics, medical characteristics, comorbidities, specific organisms, antibiotic classes, and mortality outcomes (30-day, 90-day, and 365-day mortality) is presented as number (percentage), while continuous variables are presented as mean (standard deviation). Bivariate, multinomial logistic regression was used to show the unadjusted relationship between epidemiologic location of onset and several categorical characteristics. Continuous variables in bivariate analysis were compared using Student's t-test or Wilcoxon 2-sample test dependent on the distribution of the variables. As multiple comparisons were being made, a Bonferroni correction was performed bringing the p-value considered statistically significant to $\alpha=0.0167$.(32)

A multivariable, multinomial logistic regression model was used to identify independent factors associated with having a MDRGNO versus non-MDRNGO culture. The most parsimonious model was used, with only covariates with $p<0.0167$ in bivariate analysis included in the multivariable analysis. The adequacy of the final model was tested with the -2 Log Likelihood test, AIC value, and Hosmer–Lemeshow goodness of fit. A sensitivity analysis was conducted including the first positive MDRGNO culture, as several patients had multiple cultures causing clustering within patients. A similar multinomial logistic regression model was assessed. All tests were two-tailed and a significance value of $p<0.0167$ was considered statistically significant unless otherwise noted. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

Results

Overview of MDRGNO in persons with SCI

Between January 1, 2012 and December 31, 2013, a total of 19,567 patients with SCI/D received care at a VA facility. After identification of "true infection" and elimination of non-MDR cultures previously explained (also detailed in **Figure 1**), the final number of cultures to be analyzed was 5,745. The breakdown for epidemiologic location of onset is as follows: 2,547 (44.3%) hospital-acquired, 1,989 (34.6%) healthcare-associated, and 1,209 (21.0%) community onset. The overall incidence of identified MDRGNOs over the 2 years was 20.6 positive episodes per 100 admissions (number of identified positive cultures / number of admissions). For each year, this equated to 10.3 episodes per 100 admissions. The final dataset contained a total of 2,607 patients with identified MDRGNO infections for an average of 2.2 positive cultures per patient. By location of onset, 1,294 (49.6%) patients had a hospital-acquired infection, 1,155 (44.3%) patients had a healthcare-associated infection, and 906 (34.8%) patients had a community-acquired infection (when accounting for multiple infections).

Demographics

The average age of the cohort was 61.7 years. Furthermore, the majority were male (97.3%) and just over a quarter were non-Hispanic Black (26.3). Slightly under half of the cohort had a complete injury (42.9%) with a similar number reporting tetraplegia (44.6%), while level of injury information was missing for 349 participants. Three-fifths (61.4%) of the cohort reported traumatic etiology, and the average duration for the 1,798 participants with available information was 22.4 years (809 participants had missing duration information). Over half of the participants resided in the South (+ Puerto Rico) (54.2%) while those in Northeast, Midwest, and West reported at 11.1%, 17.4%, and 17.3%, respectively. The majority of the cohort received care at a VA SCI center (61.6%) with the remaining 38.4% receiving care at a non-SCI VA facility.

Compared to those less than 50 years of age, patients 50-64 had a higher odds of having a hospital-acquired infection compared to a CAI (OR=1.45, 95% CI 1.13-1.88, p=0.004) (**Table 1**), as were patients in the 65+ age group (OR=1.59, 95% CI 1.23-2.06, p<0.0001). Additionally, those in the 50-64 and 65+ age groups had less frequent healthcare-associated infections than hospital-acquired infections, when compared to the under 50 group (OR=0.66, 95% CI 0.53-0.82, p<0.0001 and OR=0.57, 95% CI 0.46-0.72). Non-Hispanic Blacks had greater odds than Whites of experiencing a hospital-acquired infection compared to a CAI (OR=1.38, 95% CI 1.10-1.73, p<0.0001). Also, compared to Whites, Blacks had a 21% lower odds of a healthcare-associated infection compared to a hospital-acquired infection (OR=0.79, 95% CI 0.65-0.96, p=0.0005). There were no other significant differences between the other ethnic groups and Whites in epidemiologic location of onset of MDRGNOs. Males had a lower prevalence of healthcare-associated infection than hospital-acquired infection compared to females (OR=0.57, 95% CI 0.41-0.80, p=0.001), while gender was not found to be significant between healthcare-associated or hospital-acquired infection and CAIs.

Compared to incomplete (+ missing) category, complete injury reduced odds of hospital-acquired or healthcare-associated infection compared to community-acquired (OR=0.67, 95% CI 0.56-0.79, p<0.0001 and OR=0.83, 95% CI 0.72-0.95, p=0.009, respectively). Also, complete injury had increased odds of healthcare-associated infection compared to hospital-acquired, when compared to the incomplete (+ missing) category (OR=1.23, 95% CI 1.09-1.38, p=0.0008). Significant findings were also found when comparing paraplegia to tetraplegia for hospital-acquired vs CAI and healthcare-associated vs hospital-acquired, although missing data was also significant among these groups. Duration of injury for the 10-29 and 30+ categories was found to have reduced odds of hospital-acquired infection compared to CAI, when compared to the <10 + missing category (OR=0.52, 95% CI 0.41-0.67, p<0.0001 and OR=0.59, 95% CI 0.49-0.71). Furthermore, for the 10-29 and 30+ age categories, an increase in odds was found to be statistically significant for healthcare-associated infections compared to hospital-acquired (OR=1.53, 95% CI 1.22-1.90, p<0.0001 and OR=1.57, 95% CI 1.38-1.79). Neither age category was found to be significant with the reference group (<10 + missing) when comparing healthcare-associated infections to CAIs at the $\alpha=0.0167$ level (p=0.03 and p=0.35).

Etiology of SCI/D analysis found traumatic onset to have reduced odds of hospital-acquired compared to community-acquired infection and increased odds of healthcare-associated compared to hospital-acquired infection, when weighed against the non-traumatic plus missing category (OR=0.50, 95% CI 0.43-0.58, p<0.0001 and OR=1.86, 95% CI 1.54-2.10, p<0.0001). For U.S. Census region, the Midwest, South (plus Puerto Rico due to small sample size), and West compared to the Northeast were all found to have increased odds of healthcare-associated infections compared to hospital-acquired infections (OR=1.63, 95% CI 1.18-2.25, p<0.0001, OR=1.79, 95% CI 1.36-2.35, p<0.0001, and OR=2.23, 95% CI 1.62-3.08, p<0.0001). Contrarily, the South and West regions were found to have decreased odds of hospital-acquired infections compared to CAIs (with Northeast as the reference group) (OR=0.69, 95% CI 0.51-0.94, p=0.002 and OR=0.58, 95% CI 0.40-0.83, p<0.0001). No significant differences were found between healthcare-associated and CAIs between the Midwest, South, or West regions compared to the

Northeast. Being treated at a VA SCI center was associated with nearly 2.5 times the odds of hospital-acquired infection compared to a community-acquired infection, compared to those treated at a non-SCI center (OR=2.44, 95% CI 2.10-2.82, $p<0.0001$). Conversely, treatment at a SCI center resulted in reduced odds of healthcare-associated infection when compared to both hospital-acquired and community-acquired infections (OR=0.28, 95% CI 0.24-0.31, $p<0.0001$ and OR=0.67, 95% CI 0.58-0.78, $p<0.0001$, respectively).

Source of Culture

The source of MDRGNO cultures by epidemiologic location of onset is detailed in **Table 2**. As expected, the majority of hospital-acquired infection cultures were from the inpatient setting (84.3%) while cultures related to healthcare-associated infections were mainly from the outpatient setting (91.2%). For community onset infections, the great majority (81.0%) were also taken in the outpatient setting. Long-term care cultures accounted for 375 (6.5%) of the total cultures, and home care was the source for 130 (2.3%) of the cultures.

Medical Characteristics

Between the categories of epidemiologic location of onset, a number of significant associations were found with medical characteristics (detailed in **Table 3**). Compared to those cultures with community-acquired onset, hospital-acquired infections had significantly increased odds of the following medical characteristics within the past 90 days: intensive care unit admission, long-term care stay, mechanical ventilation, previous hospitalization, surgery, gastrostomy/jejunostomy. Furthermore, increased odds were found for steroid use greater than or equal to 85 days when comparing hospital-acquired infections to community onset infections. Antibiotic use in the past

90 days was not found to be significantly different for hospital-acquired infections when compared to community-acquired infections (p=0.03).

Similarly, several medical characteristics were also associated with significantly increased odds of healthcare-associated infections when compared to the community-acquired onset group. Significant associations were found for intensive care unit admission, long-term care stay, previous hospitalization, and surgery – all within the past 90 days. Additionally, antibiotic use in the previous 90 days was associated with over a five-fold increase in the odds of a healthcare-associated infection compared to the community-acquired group (OR=5.66, 95% CI 2.08-15.38, p=0.0007). When comparing healthcare-associated to community-acquired infections, no significant associations were found for mechanical ventilation (p=0.1835), steroid usage greater than or equal to 85 days (p=0.06), or gastrostomy/jejunostomy (p= 0.4349).

When compared to hospital-acquired infections, healthcare-associated infections were associated with significantly reduced odds of intensive care unit admission, long-term care stay, mechanical ventilation, previous hospitalization, surgery, and gastrostomy/jejunostomy in the past 90 days. No significant associations were found for antibiotic use in the past 90 days (p=0.05) or steroid exposure $\geq$ 85 days (p=0.06). Across all three levels of onset, no significant findings were found for urinary tract procedure in the past 90 days compared to those who did not have a urinary tract procedure.

Comorbidities

Several statistically significant findings were found between the epidemiologic location of onset of infections and comorbid conditions that were either pre-existing (within 365 days of hospitalization or outpatient encounter) or found at the time of admission. As shown in **Table 4**, when compared to community onset infections, hospital-acquired infections were associated with statistically significant increased odds of atherosclerotic peripheral vascular disease, chronic obstructive pulmonary disease, stroke/ cerebrovascular accident, dementia, diabetes, myocardial infarction, liver disease, pressure ulcers, and renal disease. No significant associations for hospital-acquired infections compared to community onset were found for cancer/ tumor ($p= 0.64$).

Oppositely, several statistically significant associations of decreased odds were found when comparing healthcare-associated infections with community-acquired infections, including the following: congestive heart failure, chronic obstructive pulmonary disease, stroke/ cerebrovascular accident, diabetes, liver disease, pressure ulcers, and renal disease. No findings were significant at the $\alpha=0.0167$ level for APVD, dementia, and myocardial infarction when comparing healthcare-associated infections with those acquired in the community. Likewise, significant decreased odds were also observed when comparing healthcare-associated infections to the hospital-acquired onset group for all comorbidities except for acquired immunodeficiency syndrome (AIDs) and arthritis (both of which had small sample sizes and were not analyzed). When comparing healthcare-associated to hospital-acquired infections, pressure ulcers were particularly significant, with nearly a 90% decreased odds of comorbid pressure ulcers compared to the no pressure ulcer group (OR=0.12, 95% CI 0.11-0.14, $p <0.0001$).

Specific Organisms

Several causative pathogens were examined for possible associations between MDRGNOs and onset site, shown in **Table 4**. Of the cultures, 4,993 (86.9%) were a type of *Enterobacteriaceae* while *Pseudomonas Aeruginosa, Acinetobacter,* and *Other Gram-Negatives* accounted for 18.6%, 4.3% and 1.4% of positive cultures, respectively (cultures can have more than one causative organism). When compared to community onset infections, *Proteus mirabilis, Pseudomonas aeruginosa,* and *Acinetobacter* resulted in an increased odds of hospital-acquired infection, with *Acinetobacter* having nearly a three-fold increase in odds (OR=2.89, 95% CI 1.94-4.31, p<0.0001). Similarly, when healthcare-associated infections were compared to hospital-acquired infections, a decrease in odds was found for the same pathogens (*Proteus mirabilis, Pseudomonas aeruginosa,* and *Acinetobacter*).

Conversely, the causative organism that resulted in associations opposite of those listed above was *Escherichia coli*. Compared to community onset infections, *E. coli* resulted in a decrease in odds of hospital-acquired infections (OR=0.43, 95% CI 0.38-0.50 p<0.0001); likewise, when compared to hospital-acquired infections, *E. coli* lead to an increased odds of healthcare-associated infections (OR=2.25, 95% CI 1.99-2.53, p<0.0001). No significant associations were found between MDRGNO infection and epidemiologic location of onset for *Klebsiella pneumonia*, 'other *Enterobacteriaceae'*, or 'other gram-negative' groups. Moreover, while 1,372 (23.9%) cultures were flagged as polymicrobial, no significant associations were found by epidemiologic location of onset. No significant associations were found when comparing the healthcare-associated infections to the CAIs.

Antibiotic Usage

Antibiotic classes were broken down to investigate the association between previous antibiotic exposure and site of onset of MDRGNOs (results available in **Table 5**). Nearly all (99.3%) of the identified infections in the cohort reported antibiotic exposure in the 90 days prior to culture date. For *Fluoroquinolones,* which made up 47.9% of the cohort, significant differences were found when comparing hospital-acquired vs. community onset and healthcare-associated vs. community onset. However, no significant associations were found between the hospital-acquired and healthcare-associated groups for *Fluoroquinolones* (p=0.53). For *Cephalosporins*, significant associations were found for *1st and 2nd* generations of the antibiotic for both hospital-acquired and healthcare-associated infections when compared to the community onset group; for the *3rd and 4th generation Cephalosporins*, all three epidemiologic location of onset comparisons were found to be significant.

When compared to the community onset group, hospital-acquired infections resulted in significantly increased odds for 14 of the 19 antibiotics groupings studied, with *Vancomycin* and *Carbapenems* each resulting in over a 5-fold increase in odds (OR=5.89, 95% CI 4.93-7.03, p<0.0001 and OR=5.18, 95% CI 4.15, 6.48, p<0.0001). The only antibiotic resulting in a decreased in odds when comparing hospital-acquired infections to community onset was Nitrofuran (OR=0.33, 95% CI 0.27-0.40, p<0.0001). In addition to the associations found for *Fluoroquinolone* and *Cephalosporins*, significant associations were found for *Carbapenems, Aminoglycosides*, and *Vancomycin* when comparing healthcare-associated infections to community onset. Twelve of the nineteen antibiotics resulted in a significantly decreased odds of healthcare-associated infection compared to hospital-acquired, with only *Sulfonamides* and

Nitrofuran resulting in an increased odds of infection ($p<0.0001$ for both). No significant associations were found for *Fosfomycin* or *Trimethoprim* for any setting of onset comparison.

Adjusted Model

All demographics, medical characteristics, and comorbidities that met the threshold of $p<0.0167$ were included in the model. Although significant, previous hospitalization was removed due to collinearity with intensive care unit admission and surgery. In all, nineteen variables were included in the final model (available in **Table 6**). Consistent with the unadjusted analyses, healthcare-associated compared to hospital-acquired infections resulted in increased odds of paraplegia, traumatic onset, and a duration of 30+ years (when compared to reference of less than 10 years). However, duration of 10-29 years was no longer found to be significant in the adjusted model ($p=0.14$). Also consistent were reduced odds of hospital-acquired infection for paraplegia, traumatic onset, and duration groups 10-29 and 30+ (when compared to <10 years) when compared to CAIs and adjusted for the other factors. Consistent with the unadjusted findings, no significant differences were found for level, duration, or etiology of injury when comparing healthcare-associated to community-acquired infections.

Following what was shown in the unadjusted models, U.S. Census region was also associated with epidemiologic location of onset of MDRGNO infections in the adjusted analysis. When compared to the Northeast region, the South, Midwest, and West all had increased odds of healthcare-associated infections compared to hospital-acquired setting of onset. Similarly, both the South and West regions saw a reduced frequency of hospital-acquired infections compared to CAIs, when adjusted for the other factors. Also in concordance with the unadjusted models, there were no differences between healthcare-associated and CAIs for Census regions, when compared to the Northeast. When compared to no SCI center, being treated at a SCI center resulted in reduced odds of healthcare-associated infection versus both hospital-acquired and community onset infections. After model adjustment, being treated at an SCI center increased the odds of hospital-acquired versus community-acquired infection by 50% from the unadjusted model, resulting in nearly a three-fold increase in the odds of hospital-acquired infection (UOR= 2.44, 95% CI 2.10, 2.82 and AOR=2.91, 95% CI 2.34-3.46).

Consistent with unadjusted analyses, healthcare-associated infections had significantly reduced odds of intensive care unit admission, long-term care stay, mechanical ventilation, surgery, CHF, COPD, stroke, diabetes, myocardial infarction, liver disease, cancer, pressure ulcers, and renal disease compared to hospital-acquired infections, with pressure ulcers producing the lowest odds of healthcare-associated infection (OR=0.13, 95% CI 0.11-0.15, $p<0.0001$). Similarly, unadjusted-consistent decreases in odds were also seen when comparing healthcare-associated to the community onset group for intensive care unit admission, long-term care stay, surgery, COPD, stroke, diabetes, liver disease, pressure ulcers, renal disease, and cancer (CHF was no longer significant in the adjusted model). Furthermore, comparing healthcare-associated to the community onset group was the only setting of onse comparison to be significant for antibiotic use in the past 90 days, with over a 4-fold increase in odds (OR=4.82, 95% CI 1.74-13.36, $p=0.003$).

When compared to community onset infections, an increase in odds of hospital-acquired infections was seen for intensive care unit admission, long-term care stay, mechanical ventilation, surgery, COPD, stroke, pressure ulcer, and renal disease, with long-term care stay, mechanical ventilation, and surgery all resulting in over a 3-fold increase in event frequency (OR=4.53, 95% CI 2.76-7.42, p<0.0001, OR=3.53, 95% CI 2.34-5.33, p<0.0001, and OR=3.34, 95% CI 2.47-4.51, p<0.0001, respectively). After adjusting for the other factors in the model, CHF, diabetes, myocardial infarction, and liver disease were no longer significant when comparing hospital and community onset groups (p=0.02, p=0.02, p=0.02, and p=0.06, respectively).

Sensitivity Analysis

A sensitivity analysis was performed to test the appropriateness of the full, adjusted model detailed above. For the analysis, the first culture of each patient was assessed with the nineteen variables included in the adjusted model. After removing multiple cultures per patient, the total number of cultures (and participants) was 2,607. Between the full model and the model reduced to participants, the point estimates varied little (available in **Appendix B**). However, due to the small sample size, confidence intervals increased in the reduced model causing several variables to no longer be significant (such as the two duration categories when comparing hospital-acquired to community-acquired). As the point estimates changed very little, it was assumed that repeated infection in the same patient demonstrated similar characteristics (low within person variability), and it was decided to use the full model as the final model.

All-Cause Mortality

Outcomes of 30, 90, and 365-day mortality were assessed with the epidemiologic location of onset of MDRGNO infections. As multiple cultures per patient were possible, the first culture of each patient was used to assess mortality, bringing the total cultures to N=2,607. Overall 30-day, 90-day, and 1-year mortality were 3.4% (89 participants, 7.0% (182 participants), and 16.7% (435 participants), respectively. Compared to the community onset group, there was over a two-fold increase in odds of mortality in the hospital-acquired group, except in 30-day mortality, where hospital and community onset were similar (p= 0.08). Across all three levels of mortality, healthcare-associated onset resulted in reduced odds of mortality compared to hospital-acquired infections. There was no significant difference in healthcare-associated and community onset mortality (**Table 7**).

Discussion

This study represents a robust evaluation of risks and characteristics of MDRGNOs relative to epidemiologic location of onset site. Gram-negative bacteria and resistance has been increasing within the SCI/D population over the past decade.(33) Of the 12,232 GN cultures that were identified as 'true' infection in this study, 47.0%(5,745) cultures were flagged as multidrug resistant. A total of 4,536 cultures (79.0%) were labeled as either hospital-acquired or healthcare-associated, which is likely the result of increased health services of individuals with spinal cord injuries.(2) Moreover, urine cultures accounted for 89.2% of total cultures, which fits with past research showing the average spinal cord injured patient has 2.5 urinary tract infections per year.(34)

The main findings of this study are overall consistent with the literature, however, a few results were surprising. Several associations were found between epidemiologic location of onset and medical characteristics. An intensive care unit admission in the previous 90 days was significantly more frequent among hospital-acquired infections than healthcare-associated and community-acquired infections (23.7% vs. 7.6% and 5.1%). Intensive care unit stays have been found to significantly increase the risk of nosocomial gram-negative infections.(35,36) These results from previous studies are consistent with the findings of this study, which shows a high rate of infection within the hospital-acquired group. As urinary tract infections are the most frequent secondary health condition for people with SCI, it was unsurprising to see approximately 5% of the study population had a urinary tract procedure in the 90 days before culture date. However, there were no statistical differences between the onset groups, which may reflect the increasing presence of procedures done outside of the hospital setting.(37) Also, nearly the whole cohort studied (99.3%) reported antibiotic use in the 90 days before culture. This is likely the result of the 'true' infection definition defined in this study that excluded patients who did not have incident antibiotic use (± 7 days of culture date).

A large number of comorbid conditions existed within this population, which can increase interactions with the healthcare system. The most prevalent comorbidity seen within this study was pressure ulcers, with 36.5% of all cultures related to this comorbidity. Pressure ulcers typically result from a lack of movement within the SCI population, and they are a known risk factor for the development of infections.(38) Furthermore, diabetes was prevalent for 16.0% of cultures within this cohort, which is consistent with research showing a strong association between type 2 diabetes and SCI.(39) Diabetes can result from the abnormalities of carbohydrate and lipid metabolism commonly seen within patients as a result of SCI.(40) Both pressure ulcers and diabetes were seen significantly more often in hospital-acquired infections than healthcare-associated and community-acquired infections (57.0% and 22.3%). Pressure ulcers and/or diabetes can be the reason for an admission, and each have the potential to cause extended hospital stays and/or procedures to control the comorbidities.(41)

The most common organism seen in the cohort was *E. coli*, which was present in 43.7% of all cultures. There was no difference in the frequency of *E. coli* in healthcare-associated and community-acquired infections (p=0.6608), with approximately 52% of both onset groups reporting *E. coli* as a causative agent. This is consistent with past literature showing high frequency among community infections (42), although less research has been done on healthcare-associated MDRGNOs. Also consistent with existing literature, hospital-acquired infections were statistically less frequent for infections caused by *E. coli* (43). Hospital-acquired infections, though, did see a statistically higher prevalence of *Acinetobacter* than healthcare-associated and community-acquired infections (p<0.0001 for both comparisons). This is consistent with literature showing that *Acinetobacter*-related infections often result from prolonged hospitalization, with only a small number of infections found in the general community.(44)

Furthermore, nearly a quarter (23.9%) of cultures were found to be polymicrobial. Across the three onset categories, no statistically significant differences were found among those cultures found to be polymicrobial. Past evidence has suggested most polymicrobial infections have a nosocomial origin.(45) However, the high rate of polymicrobal infections also found in healthcare-associated and community-acquired infections is consistent with emerging evidence of polymicrobial infections, such as pneumonia, becoming more prevalent in community-acquired infections.(46)

Among 30-day, 90-day, and 1-year mortality levels, hospital-acquired infections experienced frequencies about double those of healthcare-associated and community-acquired, which is consistent with past literature on mortality and epidemiologic location of onset.(45) Conversely, the differences between healthcare-associated and community-acquired infections were significant at the 30-day mark, but then the association appears to dissipate throughout the year of follow-up.

Although healthcare-associated and community-acquired infections are often grouped together, this study presents several significant differences between the two groups. Healthcare-associated infections were found to be at greater risk of intensive care unit admission, long-term care stay, antibiotic use, and surgery, when compared to community-acquired infections. Additionally, healthcare-associated infections were found to have a protective effect for several comorbidities compared to community onset, such as COPD, stroke, and liver disease. Consistent with findings from Horcajada et al. (2013), healthcare-associated onset is often an under-recognized onset group, with its own, distinctly associated demographic and medical characteristics.(47,48)

Limitations

This study was retrospective and did not include a medical record review. Thus, there may be issues with the reliability of coding certain procedures and unavailability of clinical data that may have further demonstrated severity of illness. The data used in this study is now five years old. Since MDRGNOs have been increasing in prevalence since 2013 (20), this study may underrepresent the current associations in this population. In addition, the study was over 96% male, which may limit the generalizability of the study; nevertheless, the spinal cord injury population is overwhelming male.(1) Furthermore, the attempt to classify true infections and narrow down positive cultures may have inaccurately captured urinary tract, bloodstream, and respiratory infections. Lastly, statistical capabilities hindered the ability to account for recurrent infections within the adjusted model. However, as discussed in the sensitivity analysis section, point estimates were found to be similar.

Implications / Future Directions

The increasing threat of MDRGNOs and the growing burden on physicians, patients, and the entire healthcare system as a whole have resulted in MDRGNOs becoming a top safety priority, according to the Centers for Disease and Control.(49) To my knowledge, this is the first study investigating the epidemiologic location of onset of MDRGNO urinary, bloodstream, and respiratory infections in the SCI/D population. As a leader in SCI/D, the VA was well poised to study the epidemiologic location of onset of MDRGNOs within this population.

In the future, research should be conducted to break down healthcare-associated location of onset into further categories (hospital, long-term care, home health, etc.) to see if trends emerge. Additionally, other outcomes of interest should be investigated, such as length of stay and recurring infections. As the number of MDRGNOs have been increasing each year (14), emerging knowledge in this field will be imperative to combat the growing strain MDRGNOs place on the healthcare system. With increased knowledge of the risk factors of MDRGNOs by epidemiologic location of onset, targeted prevention and treatment strategies of MDRGNOs can be developed and tested.

Conclusion

If current trends continue, MDRGNOs will likely remain an increasing threat across the globe, particularly within the SCI/D population. Hospital-acquired, healthcare-associated, and community-acquired infections vary by many demographic and medical characteristics, concurrent comorbidities, and causative organisms. Healthcare providers should stay cognizant of the frequency of MDRGNOs when treating individuals with SCI/D due to the high prevalence. Targeted therapies and prevention strategies may be necessary to combat the escalating burden MDRGNOs pose for providers, patients, and the entire healthcare system.

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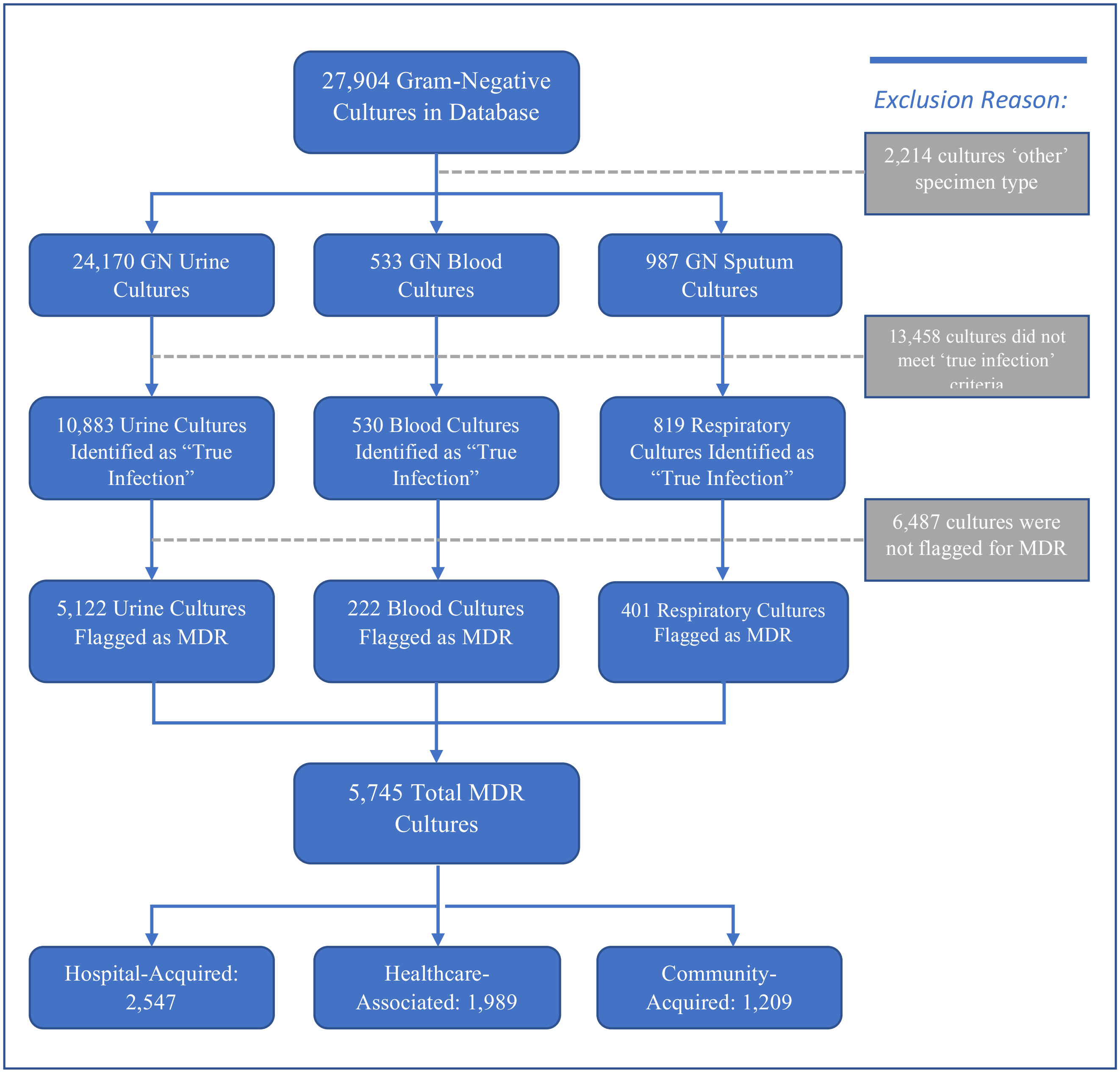
Figure 1: Flowchart of Culture Selection



Note: 'True infection' defined as positive culture and incident antibiotic use (± 7 days)

Table 1: Demographics and Factors Predisposing to Multidrug-Resistant Gram-Negative Organisms by Epidemiologic Location of Onset of Infection						
	Frequency (%)			P-Value[a]		
Demographic Characteristics	Hospital-Acquired MDRGNO (N=2,547)	Healthcare-Associated MDRGNO (N=1,989)	Community Onset MDRGNO (N=1209)	Healthcare-Associated vs. Hospital-Acquired	Hospital-Acquired vs. Community Onset	Healthcare-Associated vs. Community Onset
Age (Years)						
18-49	287 (11.3)	340 (17.1)	195 (16.1)	Reference	Reference	Reference
50-64	1179 (46.3)	917 (46.1)	551 (45.6)	<0.0001	0.004	0.6570
65+	1081 (42.4)	732 (36.8)	463 (38.3)	<0.0001	<0.0001	0.3636
Mean (SD)	62.7 (12.6)	60.7 (12.5)	61.0 (13.0)	<0.0001	<0.0001	0.5052
Race/Ethnicity						
White	1390 (54.6)	1176 (59.1)	717 (59.3)	Reference	Reference	Reference
Hispanic	175 (6.9)	136 (6.8)	100 (8.3)	0.4826	0.4432	0.1808
Black	829 (32.6)	554 (27.9)	311 (25.7)	0.0005	<0.0001	0.3327
Other	61 (2.4)	46 (2.3)	29 (2.4)	0.5637	0.7230	0.8900
Unknown	92 (3.6)	77 (3.9)	52 (4.3)	0.9460	0.6104	0.5818
Gender						
Female	60 (2.4)	81 (4.1)	34 (2.8)	Reference	Reference	Reference
Male	2487 (97.6)	1908 (95.9)	1175 (97.2)	0.0011	0.4021	0.0652
Level of Injury						
Tetraplegia	1271 (49.9)	929 (46.7)	539 (44.6)	Reference	Reference	Reference
Paraplegia	895 (35.1)	882 (44.3)	571 (47.2)	<0.0001	<0.0001	0.1508
Unknown	381 (15.0)	178 (9.0)	99 (8.2)	<0.0001	<0.0001	0.7571
Completeness of Injury						
Incomplete (+ Missing)	1521 (59.7)	1089 (54.8)	604 (50.0)	Reference	Reference	Reference
Complete	1026 (40.3)	900 (45.3)	605 (50.0)	0.0008	<0.0001	0.0085
Duration of Injury (Years)						
<10 (+ Missing)	1488 (58.4)	943 (47.4)	537 (44.4)	Reference	Reference	Reference
10-29	295 (11.58)	285 (14.3)	205 (17.0)	<0.0001	<.0001	0.0280
30+	764 (30.0)	761 (38.3)	467 (38.6)	<0.0001	<.0001	0.3492
Mean (SD)	22.0 (15.4)	21.7 (15.4)	21.6 (14.7)	0.5671	0.5525	0.9317
Etiology of SCI/D[b]						
Non-Traumatic (+ Missing)	1175 (46.1)	628 (31.6)	362 (29.9)	Reference	Reference	Reference
Traumatic	1372 (53.9)	1361 (68.4)	847 (70.1)	<0.0001	<.0001	0.3332
Census Region						
Northeast	347 (13.6)	158 (7.9)	117 (9.7)	Reference	Reference	Reference
South (plus other[c])	1434 (56.3)	1166 (58.6)	698 (57.7)	<0.0001	0.0016	0.1043
Midwest	414 (16.3)	307 (15.4)	188 (15.6)	<0.0001	0.0316	0.2144
West	352 (13.8)	358 (18.0)	206 (17.0)	<0.0001	<0.0001	0.0927
SCI Center (Y vs. N)	1963 (77.1)	956 (48.1)	701 (58.0)	<0.0001	<0.0001	<0.0001

[a]Multinomial logistic regression, multiple comparisons adjusted significance level of p<0.0167.
[b]Abbreviations: SCI&D, spinal cord injury and disorder.
[c]Southern region includes Puerto Rico

Table 2: Source of Multidrug-Resistant Gram-Negative Organism Culture by Epidemiologic Location of Onset of Infection			
	Frequency (%)		
Source of Culture[a]	Hospital-Acquired (N=2,547)	Healthcare-Associated (N=1,989)	Community Onset (N=1209)
Outpatient	28 (1.1)	1813 (91.2)	979 (81.0)
Inpatient	2148 (84.3)	79 (4.0)	193 (16.0)
Home Care	2 (0.1)	94 (4.7)	34(2.8)
Long-Term Care	369 (14.5)	3 (0.2)	3 (0.3)
[a]Cultures are from a population with spinal cord injury/disorder			

Table 3: Medical Characteristics and Factors Predisposing to Multidrug-Resistant Gram-Negative Organisms by Epidemiologic Location of Onset of Infection						
	Frequency (%)			P-Value[a]		
Characteristics	Hospital-Acquired MDRGNO (N=2,547)	Healthcare-Associated MDRGNO (N=1,989)	Community Onset MDRGNO (N=1209)	Healthcare-Associated vs. Hospital-Acquired	Hospital-Acquired vs. Community Onset	Healthcare-Associated vs. Community Onset
Medical Characteristics						
Urinary tract procedure in previous 90 days	137 (5.4)	116 (5.8)	58 (4.8)	0.5094	0.4532	0.2117
Intensive care unit in previous 90 days	603 (23.7)	152 (7.6)	61 (5.1)	<0.0001	<0.0001	0.0046
Long-term care in previous 90 days	160 (6.3)	66 (3.3)	21 (1.7)	<0.0001	<0.0001	0.0088
Mechanical ventilation in previous 90 days	379 (14.9)	64 (3.2)	29 (2.4)	<0.0001	<0.0001	0.1835
Hospitalization in previous 90 days	1265 (49.7)	835 (42.0)	349 (28.9)	<0.0001	<0.0001	<0.0001
Surgery in previous 90 days	491 (19.3)	168 (8.5)	56 (4.6)	<0.0001	<0.0001	<0.0001
Gastrostomy/ Jejunostomy	72 (2.8)	16 (0.8)	13 (1.1)	<0.0001	0.0012	0.4349
Antibiotic Exposure within 90 days	2530 (99.3)	1984 (99.8)	1192 (98.6)	0.0543	0.0291	0.0007
Steroid Exposure >= 85 days	62 (2.4)	32 (1.6)	10 (0.8)	0.0545	0.0014	0.0645
Charlson Comorbidity Score, Mean (SD)	3.0 (1.7)	1.0 (1.5)	2.1 (1.7)	<0.0001	<0.0001	<0.0001
Comorbidities (Within 365 days prior or during admission)[b]						
AIDS[d]	17 (0.7)	6 (0.3)	4 (0.3)	0.0936	Not reported[c]	Not reported[c]
Arthritis	17 (0.7)	3 (0.2)	7 (0.6)	Not reported[c]	0.7508	Not reported[c]
Atherosclerotic Peripheral Vascular Disease	108 (4.2)	18 (0.9)	16 (1.3)	<0.0001	<0.0001	0.2662
Congestive Heart Failure	209 (8.2)	29 (1.5)	36 (3.0)	<0.0001	Not reported[c]	Not reported[c]
Chronic Obstructive Pulmonary Disease	309 (12.1)	70 (3.5)	86 (7.1)	<0.0001	<0.0001	<0.0001
Stroke/ Cerebrovascular Accident	202 (7.9)	26 (1.3)	39 (3.2)	<0.0001	<0.0001	0.0003
Dementia	44 (1.7)	10 (0.5)	7 (0.6)	0.0004	0.0068	0.7772
Diabetes	569 (22.3)	150 (7.5)	198 (16.4)	<0.0001	<0.0001	<0.0001
Myocardial Infarction	106 (4.2)	13 (0.7)	14 (1.2)	<0.0001	<0.0001	0.1362
Liver Disease	164 (6.4)	29 (1.5)	49 (4.1)	<0.0001	0.0034	<0.0001
Pressure Ulcer	1451 (57.0)	278 (14.0)	368 (30.4)	<0.0001	<0.0001	<0.0001
Renal Disease	302 (11.9)	39 (2.0)	61 (5.1)	<0.0001	<0.0001	<0.0001
Gastrointestinal Ulcer	29 (1.1)	7 (0.4)	3 (0.3)	0.0051	Not reported[c]	Not reported[c]
Cancer/Tumor	129 (5.1)	32 (1.6)	57 (4.7)	<0.0001	0.6441	<0.0001

[a]Multinomial logistic regression multiple comparisons adjusted significance level of p<0.0167.
[b]Only those conditions with greater than five observations in at least one category are reported.
[c]P-values not reported because of small sample size comparisons or zero cells.
[d]Abbreviations: AIDS, acquired immunodeficiency syndrome.

Table 4: Causative Pathogens and Multidrug-Resistant Gram-Negative Organisms by Epidemiologic Location of Onset of Infection						
	Frequency (%)			P-Value[a]		
Characteristics	Hospital-Acquired MDRGNO (N=2,547)	Healthcare-Associated MDRGNO (N=1,989)	Community Onset MDRGNO (N=1209)	Healthcare-Associated vs. Hospital-Acquired	Hospital-Acquired vs. Community Onset	Healthcare-Associated vs. Community Onset
Specific Organisms						
All Enterobacteriaceae	2081 (81.7)	1814 (91.2)	1098 (90.8)	<0.0001	<0.0001	0.7130
Escherichia coli	832 (32.7)	1037 (52.1)	640 (52.9)	<0.0001	<0.0001	0.6608
Proteus mirabilis	577 (22.7)	355 (17.9)	222 (18.4)	<0.0001	0.0027	0.7139
Klebsiella pneumoniae	544 (21.4)	380 (19.1)	219 (18.1)	0.0616	0.0211	0.4862
Other Enterobacteriaceae	488 (19.2)	339 (17.0)	216 (17.9)	0.0672	0.3426	0.5516
Pseudomonas aeruginosa	580 (22.8)	301 (15.1)	185 (15.3)	<0.0001	<0.0001	0.8975
Acinetobacter	169 (6.6)	48 (2.4)	29 (2.4)	<0.0001	<0.0001	0.9793
Other Gram-Negatives[b]	41 (1.6)	27 (1.4)	14 (1.2)	0.4884	0.2838	0.6273
Polymicrobial	640 (25.1)	449 (22.6)	283 (23.4)	0.0458	0.2528	0.5864

[a]Multinomial logistic regression, multiple comparisons adjusted significance level of p<0.0167.
[b]Other gram-negative organisms include Achromobacter, Aeromonas, Agrobacterium, Alcaligenes, anaerobes, Bacteroides, Bordetella bronch- iseptica, Burkholderia cepacia, Chryseobacterium, Comamomas testos- teroni, Cupriavidus, Delftia acidovorans, Elizabethkingia, Fusobacterium, gram-negatives, Haemophilus, Moraxella, Myroides, Pantoea, Pasteurella, Porphyromonas, Prevotella, Rahnella, Ralstonia, Raoultella, Sphingomonas, and Stenotrophomonas maltophilia.

Table 5: Antibiotic Classes and Multidrug-Resistant Gram-Negative Organisms by Epidemiologic Location of Onset of Infection						
	Frequency (%)			P-Value[a]		
Characteristics	Hospital-Acquired MDRGNO (N=2,547)	Healthcare-Associated MDRGNO (N=1,989)	Community Onset MDRGNO (N=1209)	Healthcare-Associated vs. Hospital-Acquired	Hospital-Acquired vs. Community Onset	Healthcare-Associated vs. Community Onset
Medication exposure within 90 days						
Any antibiotic	2530 (99.3)	1984 (99.8)	1192 (98.6)	0.0543	0.0291	0.0007
Fluoroquinolones	1244 (48.8)	990 (49.7)	515 (42.6)	0.5333	0.0003	<0.0001
1st-/2nd-generation cephalosporins	449 (17.6)	339 (17.0)	151 (12.5)	0.6061	<.0001	0.0006
3rd-/4th-generation cephalosporins	993 (39.0)	459 (23.1)	224 (18.5)	<0.0001	<0.0001	0.0024
Penicillins	589 (23.1)	394 (19.8)	232 (19.2)	0.0072	0.0065	0.6685
Extended-spectrum penicillins	1003 (39.4)	342 (17.2)	140 (11.6)	<0.0001	<0.0001	<0.0001
Carbapenems	799 (31.4)	252 (12.7)	98 (8.1)	<0.0001	<0.0001	<0.0001
Vancomycin	1284 (50.4)	409 (20.6)	178 (14.7)	<0.0001	<0.0001	<0.0001
Tetracycline	300 (11.8)	179 (9.0)	100 (8.3)	0.0026	0.0012	0.4793
Nitrofuran	238 (9.3)	525 (26.4)	287 (23.7)	<0.0001	<0.0001	0.0943
Aminoglycosides[b]	494 (19.4)	173 (8.7)	74 (6.1)	<0.0001	<0.0001	0.0084
Metronidazole	480 (18.9)	113 (5.6)	50 (4.1)	<0.0001	<0.0001	0.0550
Sulfonamides	614 (24.1)	606 (30.5)	324 (26.8)	<0.0001	0.0750	0.0268
Daptomycin	179 (7.0)	25 (1.3)	11 (0.9)	<0.0001	<0.0001	0.3709
Erythromycin	215 (8.4)	80 (4.0)	54 (4.5)	<0.0001	<0.0001	0.5429
Clindamycin	156 (6.1)	93 (4.7)	46 (3.8)	0.0341	0.0035	0.2427
Linezolid	192 (7.5)	56 (2.8)	28 (2.3)	<0.0001	<0.0001	0.3925
Colistimethate	79 (3.1)	6 (0.3)	0 (0)	<0.0001	Not reported[c]	0.9526

[a]Multinomial logistic regression, cluster-adjusted significance level of $p<0.0167$.
[b]Includes both aminoglycosides and gentamycin.
[c]P-values not reported because of small sample size comparisons or zero cells.
[d]Antibiotics fosfomycin and trimethoprim were found to have no significance at the $\alpha=0.0167$ level.

Table 6: Multivariable Analysis of Risk Factors for Multidrug-Resistant Gram-Negative Organisms by Epidemiologic Location of Onset of Infection in Patients with SCI/D			
	Healthcare-Associated vs. Hospital-Acquired	Hospital-Acquired vs. Community Onset	Healthcare-Associated vs. Community Onset
Characteristics	Adjusted Odds Ratio (95% CI[b])	Adjusted Odds Ratio (95% CI[b])	Adjusted Odds Ratio (95% CI[b])
Level of Injury			
Tetraplegia	Reference	Reference	Reference
Paraplegia	1.25 (1.03, 1.51)	0.75 (0.61, 0.91)	0.93 (0.77, 1.13)
Unknown	0.81 (0.58, 1.13)	1.23 (0.86, 1.78)	1.00 (0.68, 1.46)
Duration of Injury (Years)			
<10 (+ Missing)	Reference	Reference	Reference
10-29	1.19 (0.90, 1.59)	0.66 (0.49, 0.88)	0.79 (0.60, 1.03)
30+	1.29 (1.03, 1.60)	0.78 (0.62, 0.98)	1.00 (0.80, 1.25)
Etiology of SCI/D[b]			
Non-Traumatic (+ Missing)	Reference	Reference	Reference
Traumatic	1.44 (1.22, 1.72)	0.62 (0.52, 0.74)	0.89 (0.74, 1.07)
Census Region			
Northeast	Reference	Reference	Reference
South (plus other)	1.94 (1.40, 2.71)	0.66 (0.47, 0.93)	1.29 (0.90, 1.85)
Midwest	1.53 (1.04, 2.27)	0.76 (0.51, 1.14)	1.17 (0.77, 1.77)
West	2.12 (1.43, 3.13)	0.59 (0.39, 0.88)	1.24 (0.82, 1.87)
SCI Center (Y vs. N)	0.24 (0.20, 0.28)	2.91 (2.34, 3.46)	0.69 (0.59, 0.80)
Intensive Care Unit in previous 90 days	0.59 (0.46, 0.52)	2.68 (1.99, 3.61)	1.58 (1.14, 2.20)
Long-Term Care in previous 90 days	0.43 (0.30, 0.62)	4.53 (2.76, 7.42)	1.94 (1.16, 3.26)
Mechanical Ventilation in previous 90 days	0.38 (0.28, 0.53)	3.53 (2.34, 5.33)	1.36 (0.85, 2.18)
Surgery in previous 90 days	0.65 (0.52, 0.81)	3.34 (2.47, 4.51)	2.16 (1.56, 3.00)
Antibiotic Exposure within 90 days	2.79 (0.95, 8.17)	1.73 (0.83, 3.59)	4.82 (1.74, 13.36)
Congestive Heart Failure	0.39 (0.25, 0.60)	1.61 (1.08, 2.43)	0.62 (0.37, 1.05)
Chronic Obstructive Pulmonary Disease	0.34 (0.25, 0.46)	1.49 (1.13, 1.97)	0.51 (0.36, 0.71)
Stroke/ Cerebrovascular Accident	0.17 (0.11, 0.27)	2.33 (1.58, 3.43)	0.39 (0.22, 0.66)
Diabetes	0.40 (0.32, 0.49)	1.27 (1.04, 1.55)	0.50 (0.40, 0.63)
Myocardial Infarction	0.36 (0.19, 0.70)	2.04 (1.11, 3.76)	0.74 (0.34, 1.61)
Liver Disease	0.28 (0.18, 0.43)	1.41 (0.99, 2.03)	0.39 (0.24, 0.63)
Pressure Ulcer	0.13 (0.11, 0.15)	2.96 (2.52, 3.47)	0.38 (0.32, 0.45)
Renal Disease	0.21 (0.14, 0.31)	1.92 (1.40, 2.64)	0.40 (0.26, 0.62)
Cancer/Tumor	0.41 (0.26, 0.64)	0.78 (0.54, 1.13)	0.32 (0.20, 0.51)

[a]Multinomial logistic regression, multiple comparisons adjusted significance level of $p<0.0167$.
[b]Abbreviations: SCI&D, spinal cord injury and disorder; CI, confidence interval.

Table 7: Mortality Outcome and Multidrug-Resistant Gram-Negative Infection by Epidemiologic Location of Onset of Infection						
	Frequency (%)			OR (95% CI)[a,b]		
Mortality Outcomes	Hospital-Acquired MDRGNO (N=1,089)	Healthcare-Associated MDRGNO (N=901)	Community Onset MDRGNO (N=617)	Healthcare-Associated vs. Hospital-Acquired	Hospital-Acquired vs. Community Onset	Healthcare-Associated vs. Community Onset
All-cause mortality						
30-day mortality	55 (5.1)	14 (1.6)	20 (3.2)	0.30 (0.16, 0.54)	1.59 (0.94, 2.68)	0.47 (0.24, 0.94)
90-day mortality	116 (10.7)	33 (3.7)	33 (5.4)	0.32 (0.21, 0.47)	2.11 (1.41, 3.15)	0.67 (0.41, 1.10)
365-day mortality	263 (24.2)	99 (11.0)	73 (11.8)	0.39 (0.30, 0.50)	2.37 (1.79, 3.14)	0.92 (0.67, 1.27)

[a]Multinomial logistic regression, multiple comparisons adjusted significance level of p<0.0167.
[b]Abbreviations: OR, odds ratio; CI, confidence interval.

Appendix A*:* List of antibiotics used to identify 'true infection' from positive cultures	
Urinary Tract Infections	*Respiratory Infections*
Aminopenicillin	Aminopenicillin
Penicillin	Penicillin
Extended-spectrum penicillin	Extended-spectrum penicillin
1^{st}-/2^{nd}-generation Cephalosporins	1st-/2nd-generation Cephalosporins
3^{rd}-/4^{th}-generation Cephalosporins	3rd-/4th-generation Cephalosporins
Carbapenem	Carbapenem
Aminoglycosides	Erythromycin
Clindamycin	Tetracycline
Fluoroquinolones	Aminoglycosides
Nitrofuran	Clindamycin
Sulfonamide	Fluoroquinolones
Other Anti-infect	Sulfonamide
Colistimethate	Other Anti-infect
Daptomycin	Colistimethate
Fosfomycin	Daptomycin
Gentamycin	Gentamycin
Linezolid	Linezolid
Trimethoprim	Metronidazole
Vancomycin	Trimethoprim
	Vancomycin

APPENDIX B: SENSITIVITY ANALYSIS			
	Healthcare-Associated vs. Hospital-Acquired	Hospital-Acquired vs. Community Onset	Healthcare-Associated vs. Community Onset
Characteristics[a]	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Level of Injury			
Tetraplegia	Reference	Reference	Reference
Paraplegia	1.25 (1.03, 1.51)	0.75 (0.61, 0.91)	0.93 (0.77, 1.13)
Paraplegia[b]	1.27 (0.95, 1.69)[c]	0.61 (0.45, 0.81)	0.77 (0.58, 1.02)
Unknown	0.81 (0.58, 1.13)	1.23 (0.86, 1.78)	1.00 (0.68, 1.46)
Unknown[b]	0.75 (0.46, 1.20)	1.00 (0.61, 1.64)	0.75 (0.45, 1.25)
Duration of Injury (Years)			
<10 (+ Missing)	Reference	Reference	Reference
10-29	1.19 (0.90, 1.59)	0.66 (0.49, 0.88)	0.79 (0.60, 1.03)
10-29[b]	1.08 (0.70, 1.68)	0.71 (0.46, 1.09)[c]	0.76 (0.51, 1.15)
30+	1.29 (1.03, 1.60)	0.78 (0.62, 0.98)	1.00 (0.80, 1.25)
30+[b]	1.37 (0.99, 1.89)[c]	0.83 (0.60, 1.17)[c]	1.14 (0.83, 1.57)
Etiology of SCI/D			
Non-Traumatic (+ Missing)	Reference	Reference	Reference
Traumatic	1.44 (1.22, 1.72)	0.62 (0.52, 0.74)	0.89 (0.74, 1.07)
Traumatic[b]	1.38 (1.07, 1.78)	0.55 (0.42, 0.71)	0.75 (0.58, 0.98)
Census Region			
Northeast	Reference	Reference	Reference
South (plus other)	1.94 (1.40, 2.71)	0.66 (0.47, 0.93)	1.29 (0.90, 1.85)
South (plus other)[b]	1.54 (0.95, 2.50)[c]	0.77 (0.48, 1.23)	1.18 (0.73, 1.92)
Midwest	1.53 (1.04, 2.27)	0.76 (0.51, 1.14)	1.17 (0.77, 1.77)
Midwest[b]	1.21 (0.69, 2.11)	0.96 (0.55, 1.68)	1.16 (0.66, 2.05)
West	2.12 (1.43, 3.13)	0.59 (0.39, 0.88)	1.24 (0.82, 1.87)
West[b]	2.24 (1.28, 3.93)	0.68 (0.38, 1.20)[c]	1.51 (0.86, 2.66)
SCI Center (Y vs. N)	0.24 (0.20, 0.28)	2.91 (2.34, 3.46)	0.69 (0.59, 0.80)
SCI Center (Y vs. N)[b]	0.26 (0.20, 0.33)	2.54 (1.98, 3.26)	0.65 (0.52, 0.81)
Intensive Care Unit in previous 90 days	0.59 (0.46, 0.52)	2.68 (1.99, 3.61)	1.58 (1.14, 2.20)
Intensive Care Unit in previous 90 days[b]	0.61 (0.40, 0.92)	2.59 (1.56, 4.31)	1.63 (0.93, 2.87)
Long-Term Care in previous 90 days	0.43 (0.30, 0.62)	4.53 (2.76, 7.42)	1.94 (1.16, 3.26)
Long-Term Care in previous 90 days[b]	0.37 (0.21, 0.66)	3.87 (2.00, 7.49)	1.43 (0.70, 2.93)[c]
Mechanical Ventilation in previous 90 days	0.38 (0.28, 0.53)	3.53 (2.34, 5.33)	1.36 (0.85, 2.18)
Mechanical Ventilation in previous 90 days[b]	0.25 (0.13, 0.45)	3.37 (1.81, 6.27)	0.83 (0.38, 1.80)
Surgery in previous 90 days: Any	0.65 (0.52, 0.81)	3.34 (2.47, 4.51)	2.16 (1.56, 3.00)
Surgery in previous 90 days: Any[b]	0.49 (0.35, 0.69)	4.02 (2.57, 6.29)	1.97 (1.21, 3.20)
Antibiotic Exposure within 90 days	2.79 (0.95, 8.17)	1.73 (0.83, 3.59)	4.82 (1.74, 13.36)

Antibiotic Exposure within 90 days[b]	1.66 (0.51, 5.41)	2.53 (1.05, 6.05)	4.18 (1.47, 11.93)
Congestive Heart Failure	0.39 (0.25, 0.60)	1.61 (1.08, 2.43)	0.62 (0.37, 1.05)
Congestive Heart Failure[b]	0.20 (0.09, 0.45)	1.47 (0.85, 2.54)[c]	0.30 (0.13, 0.70)[c]
Chronic Obstructive Pulmonary Disease	0.34 (0.25, 0.46)	1.49 (1.13, 1.97)	0.51 (0.36, 0.71)
Chronic Obstructive Pulmonary Disease[b]	0.33 (0.20, 0.52)	1.23 (0.83, 1.81)[c]	0.40 (0.24, 0.66)
Stroke/ Cerebrovascular Accident	0.17 (0.11, 0.27)	2.33 (1.58, 3.43)	0.39 (0.22, 0.66)
Stroke/ Cerebrovascular Accident[b]	0.16 (0.07, 0.34)	3.04 (1.63, 5.69)	0.48 (0.20, 1.15)[c]
Diabetes	0.40 (0.32, 0.49)	1.27 (1.04, 1.55)	0.50 (0.40, 0.63)
Diabetes[b]	0.37 (0.27, 0.52)	1.21 (0.91, 1.61)[c]	0.45 (0.32, 0.64)
Myocardial Infarction	0.36 (0.19, 0.70)	2.04 (1.11, 3.76)	0.74 (0.34, 1.61)
Myocardial Infarction[b]	0.25 (0.08, 0.83)	2.03 (0.83, 5.00)[c]	0.52 (0.14, 1.86)
Liver Disease	0.28 (0.18, 0.43)	1.41 (0.99, 2.03)	0.39 (0.24, 0.63)
Liver Disease[b]	0.36 (0.19, 0.67)	1.36 (0.82, 2.28)	0.49 (0.25, 0.95)
Pressure Ulcer	0.13 (0.11, 0.15)	2.96 (2.52, 3.47)	0.38 (0.32, 0.45)
Pressure Ulcer[b]	0.14 (0.11, 1.18)	2.75 (2.17, 3.47)	0.39 (0.29, 0.50)
Renal Disease	0.21 (0.14, 0.31)	1.92 (1.40, 2.64)	0.40 (0.26, 0.62)
Renal Disease[b]	0.36 (0.21, 0.60)	2.05 (1.30, 3.26)	0.73 (0.41, 1.31)[c]
Cancer/Tumor	0.41 (0.26, 0.64)	0.78 (0.54, 1.13)	0.32 (0.20, 0.51)
Cancer/Tumor[b]	0.43 (0.24, 0.76)	0.82 (0.52, 1.30)	0.34 (0.19, 0.63)

[a]First entry denotes adjusted model with repeated cultures included (N=5,745).
[b]Second entry denotes adjusted model with only first culture of participants included (N=2,607).
[c]Denotes a change in significance ($p<0.0167$) in reduced model from the full model.
[d]Abbreviations: CI, confidence interval.