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Major Article

Risk factors for infection with multidrug-resistant organisms in Haryana, India

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Background: The objective of this study was to investigate risk factors for multidrug-resistant organism (MDRO) infection within patients from a tertiary care hospital in Northern India. This case-control study examined MDRO infection risk factors, including diet, health history, and medical device use. We administered a diet questionnaire to collect data on usual diet and collected data on other risk factors from chart review. All participants were inpatients identified through hospital microbiology reports. A total of 39 MDRO patient cases and 91 controls were included.

Methods: Descriptive statistics, univariate analysis, and multivariate logistic regression were performed to evaluate the association between risk factors and MDRO infection.

Results: All cases had gram-negative MDRO infections. Univariate analyses found length of hospital stay, connective tissue disease, hospitalization in the last 12 months, hospitalization of a family member, in-hospital antibiotic use, antibiotic use in the last 12 months, and feeding tube, central venous line, and urinary catheter use to be significantly different between cases and controls. Logistic regression showed a >3-fold increase in the odds of infection with antibiotic use in the last 12 months (odds ratio [OR], 3.30; 95% confidence interval [CI], 1.22-8.91) and urinary catheter use (OR, 3.63; 95% CI, 1.14-11.58). Differences in dietary preferences and fruit, vegetable, and fiber consumption were not significantly associated with infection.

Conclusions: Antibiotic use is a major driver of MDRO infections. Our findings suggest that interventions optimizing antibiotic stewardship and reducing device use should be a priority to prevent MDRO infections.

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Antibiotic resistance is a major threat to human health across the globe and is rapidly becoming more common.[1] Multidrug-resistant organisms (MDROs) causing infections have been rising over the last few decades worldwide. The high prevalence of MDROs such as vancomycin-resistant *Enterococcus* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), resistant gram-negative bacteria, and *Clostridium difficile* has had a dramatic and widespread effect on human health. Preventing these infections is a major priority of international and national health agencies.

The Center for Disease Dynamics, Economics and Policy reported in their 2015 report on the state of the world's antibiotics that the incidence of infections from MDROs, such as MRSA, is rapidly rising worldwide.[2] The burden of antimicrobial resistance in low-income countries is several times higher than in high-income nations.[2] In India, this is a particularly prevalent problem. Many infants in the country are now born with infections resistant to most known types of antibiotics.[3] MDRO infections among this vulnerable population has greatly increased infant mortality rates, so that

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nearly one-third of the world's newborn deaths occur in India each year.[4] Although there is significant research regarding antibiotic resistance and the impact of MDROs in high-income countries, research on the causes, determinants, and solutions for MDROs in low- and middle-income countries, such as India, is limited.

Understanding the pathogenesis and risk factors for acquisition of MDROs in these populations is important for devising context-specific strategies for prevention. The niche for many MDROs is the gastrointestinal tract. There is an elaborate and complex ecosystem of anaerobic bacteria within the human gastrointestinal system. The survival and composition of this bacterial community depends on many factors, including perinatal factors, diet, age, sex, and antibiotic exposure.[5-7] In healthy individuals, mutualistic gastrointestinal microbes can provide an effective defense against invading pathogenic bacteria, including MDROs.[8,9] However, if an imbalance in the microbial composition occurs, individuals can become more vulnerable to acquiring MDROs. Disruption of the microbiome can subsequently lead to both acute and chronic disease states.

Other risk factors for MDROs include advanced age, chronic illness, severe illness, hospital or health care exposure, immune suppression, nutritional factors, antibiotic use, gastric acid status, and use of devices such as endotracheal tubes, intravenous catheters, urinary catheters, and feeding tubes.[10-15] Although there are many factors that contribute to the striking rise of antibiotic resistance, the regional diet and the food sources that contribute to the diet may also have an impact on the growth of MDROs.[16,17] The purpose of this study is to examine prevalence of and risk factors for infection with an MDRO in inpatients at a hospital in Haryana, India, including measurement of the known risk factors along with comparison of different components of the North Indian diet.

METHODS

Research design and methods

The study was conducted from June-July 2016 at a 1,250-bed tertiary care hospital serving a large population from the surrounding 4 states, including Jammu and Kashmir, Punjab, Uttar Pradesh, and Bihar in Northern India. Study cases were identified with the assistance of the hospital's microbiology department. They included inpatients with an MDRO infection, defined as having ≥1 of the following identified in clinical culture from blood, urine, sputum, or a wound: VRE, *C difficile*, MRSA, or gram-negative bacteria resistant to ≥3 classes of antibiotics.

The hospital's microbiology department compiled a daily list of hospitalized patients with cultures positive for MDROs. At the study site, standard bacterial culture and susceptibility testing are conducted, and *C difficile* testing is via enzyme-linked immunosorbent assay for GDH, toxin A, or toxin B, which is confirmed by polymerase chain reaction. We assessed each patient for eligibility based on inclusion and exclusion criteria. All hospital inpatients at least 18 years of age were initially eligible to participate. Exclusion criteria include inability to communicate in Hindi or English, housed in the inpatient rehabilitation or psychiatric facilities, inability to respond (ie, in a comatose state), altered mental state, or current use of a nasogastric tube at the time of interview. The hospital's dietetics department helped the research team provide information about the study to eligible potential participants. We aimed to recruit at least 2 controls for each case participant. Controls were identified by random selection from inpatient units where patients infected with MDROs were located. The same inclusion and exclusion criteria were applied to cases and controls. Records of the control participants were cross-referenced with microbiology results to ensure they did not have any MDRO-positive cultures.

We collected demographic data through chart review. Other factors with the potential to influence MDRO infection were also collected including in-hospital measures of body mass, length of hospital stay, current admission medication use including antibiotics, need for intensive care, and presence of urinary catheters, central lines, or feeding tubes, and prior to hospitalization measures taken by patient or family recall, which included medical and surgical history, personal and family prior hospital exposure, prior antibiotic and other medication use, and prior MDRO infection.

We used a diet questionnaire to assess daily food intake and eating habits of participants over the previous 12 months. The tool was a modified version of a validated diet instrument for use in and around New Delhi, India.[18] The study hospital is geographically close to New Delhi, and the cities are connected by a shared public transport subway system. The tool was reviewed and adapted with the help of the dietetics department at the study hospital. Each subject answered the questionnaire once. The questionnaire took approximately 30 minutes to complete and included questions about the types of food available to participants and how often (per day, per week, or per month) they eat each food item. We separately asked participants if they were committed to a special diet.

The University of Wisconsin-Madison and study hospital institutional review boards for human subject's research approved all protocols. Participants provided informed consent prior to study participation.

Statistical analysis

Descriptive statistics and univariate analyses were performed in Stata v.14 (StataCorp, College Station, TX). Multivariate logistic regression analysis was conducted using SAS v. 9.4 (SAS Institute, Cary, NC), with MDRO infection as the dependent variable and several potential MDRO risk factors as independent variables. The nutritional content of foods eaten by participants was calculated using the Indian Council of Medical Research[19] and the USDA National Nutrient Database for Standard Reference.[20]

Consumption of dietary fiber, fruit, and vegetables were modeled as both linear trends and in quartiles to account for any nonlinear effects. Other independent variables were included in the initial model because they were consistent with our underlying conceptual model (age, sex, vegetarianism, and Charlson comorbidity index) or because they were suggestive of an association with MDRO status in univariate analysis (length of hospital stay, connective tissue disease, having a family member in the hospital, antibiotic use in the last 12 months, use of a feeding tube, use of a central venous line, and use of a urinary catheter). The final models were fit using stepwise selection with P value cutoff of .20. $P \leq .05$ and 95% confidence intervals of odds ratios that do not cross 1.0 were considered statistically significant. Power calculations were done using G*Power v. 3.1 (Heinrich Heine Universitat Dusseldorf, Dusseldorf, Germany).

RESULTS

The final study population included 40 cases and 91 control participants. The most common site of a positive MDRO culture was urine, followed by wound and blood (Table 1). All but one of the cultured bacteria were in the MDRO group of resistant gram-negative bacilli, with the most prevalent being *Klebsiella pneumoniae* subsp *pneumoniae* (Table 2). Of these gram-negative bacillus isolates, 24 were in the family *Enterobacteriaceae*, and of those, 20 had documented resistance to carbepenems. There was 1 case with VRE, and no cases of MRSA- or *C difficile*–positive cultures.

Most (63%) participants were men, and the median age was 57 (interquartile range, 42-65) (Table 3). There were no significant differences in intensive care unit admissions or mean Charlson