American Journal of Infection Control 42 (2014) 626-31

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major article

Risk factors and outcomes of infections caused by extremely drug-resistant gram-negative bacilli in patients hospitalized in intensive care units

Sameer J. Patel MD, MPH [a,*], André P. Oliveira MPH [a], Juyan Julia Zhou MS, MPH [a], Luis Alba BS [a], E. Yoko Furuya MD, MS [b,c], Scott A. Weisenberg MD, MSc [d], Haomiao Jia PhD [e,f], Sarah A. Clock PhD, MPH [a], Christine J. Kubin PharmD [b,g], Stephen G. Jenkins PhD [h], Audrey N. Schuetz MD, MPH [h,i], Maryam Behta PharmD [j], Phyllis Della-Latta PhD [k], Susan Whittier PhD [k], Kyu Rhee MD, PhD [l], Lisa Saiman MD, MPH [a,c]

[a] Department of Pediatrics, Columbia University Medical Center, New York, NY
[b] Department of Medicine, Columbia University Medical Center, New York, NY
[c] Department of Infection Prevention & Control, New York-Presbyterian Hospital, New York, NY
[d] Department of Medicine, Alta Bates Summit Medical Center, Oakland, CA
[e] Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY
[f] School of Nursing, Columbia University Medical Center, New York, NY
[g] Department of Pharmacy, New York-Presbyterian Hospital, New York, NY
[h] Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, NY
[i] Clinical Microbiology Laboratory, New York-Presbyterian Hospital, New York, NY
[j] Clinical Performance Improvement, University of Pennsylvania Health System, Philadelphia, PA
[k] Department of Pathology, Columbia University Medical Center, New York, NY
[l] Department of Medicine, Weill Cornell Medical College, New York, NY

Key Words:
Antibiotic resistance
Gram-negative bacteria
Health care-associated infection
Mortality

Background: Extremely drug-resistant gram-negative bacilli (XDR-GNB) increasingly cause health care-associated infections (HAIs) in intensive care units (ICUs).

Methods: A matched case-control (1:2) study was conducted from February 2007 to January 2010 in 16 ICUs. Case and control subjects had HAIs caused by GNB susceptible to ≤1 antibiotic versus ≥2 antibiotics, respectively. Logistic and Cox proportional hazards regression assessed risk factors for HAIs and predictors of mortality, respectively.

Results: Overall, 103 case and 195 control subjects were enrolled. An immunocompromised state (odds ratio [OR], 1.55; $P = .047$) and exposure to amikacin (OR, 13.81; $P < .001$), levofloxacin (OR, 2.05; $P = .005$), or trimethoprim-sulfamethoxazole (OR, 3.42; $P = .009$) were factors associated with XDR-GNB HAIs. Multiple factors in both case and control subjects significantly predicted increased mortality at different time intervals after HAI diagnosis. At 7 days, liver disease (hazard ratio [HR], 5.52), immunocompromised state (HR, 3.41), and bloodstream infection (HR, 2.55) predicted mortality; at 15 days, age (HR, 1.02 per year increase), liver disease (HR, 3.34), and immunocompromised state (HR, 2.03) predicted mortality; and, at 30 days, age (HR, 1.02 per 1-year increase), liver disease (HR, 3.34), immunocompromised state (HR, 2.03), and hospitalization in a medical ICU (HR, 1.85) predicted mortality.

Conclusion: HAIs caused by XDR-GNB were associated with potentially modifiable factors. Age, liver disease, and immunocompromised state, but not XDR-GNB HAIs, were associated with mortality.

* Address correspondence to Sameer J. Patel, MD, MPH, 225 East Chicago Avenue, Box 20, Chicago, IL 60611.
E-mail address: sameer.patel@northwestern.edu (S.J. Patel).

Supported by the Centers for Disease Control and Prevention (R01 CI000537), the National Institute of Nursing Research (T90 NR010824; to S.A.C.), and the Clinical and Translation Science Center at Weill Cornell Medical College (KL2RR024997; to S.A.W.).
Conflicts of interest: None to report.

http://dx.doi.org/10.1016/j.ajic.2014.01.027

Antibiotic-resistant gram-negative bacilli (GNB) are increasingly common causes of health care-associated infections (HAIs) in intensive care units (ICUs)[1] and are associated with higher mortality rates, longer hospitalizations, and increased health care expenditures.[2,3] Effective treatment for extremely drug-resistant (XDR) GNB infections is challenging because of limited therapeutic options.[4]

In this study, we examined the epidemiology and outcomes of HAIs caused by XDR-GNB in the 16 ICUs affiliated with our medical center. We performed a case-control study to identify risk factors associated with XDR-GNB infections compared with non-XDR-GNB infections. We hypothesized that exposure to carbapenem agents would be associated with HAIs caused by XDR-GNB. In addition, we performed a survival analysis to explore whether predictors for death changed 7, 15, and 30 days after diagnosis of an HAI. We hypothesized that HAIs caused by XDR-GNB would be associated with an increased hazard for mortality and that the effect would be most pronounced at 7 days, rather than at 15 or 30 days.

MATERIALS AND METHODS

Study design and study setting

This study was a prospective cohort study with a nested, matched case-control study. It was conducted from February 2007 to January 2010 in the 16 ICUs affiliated with New York-Presbyterian (NYP) Hospital located in New York City. NYP is a 2,278-bed (383 ICU beds) tertiary care facility affiliated with 2 medical schools: Columbia University College of Physicians and Surgeons and Weill Cornell Medical College. Study ICUs included medical (n = 5), surgical (n = 6), burn (n = 1), and pediatric/neonatal (n = 4) ICUs and had approximately 14,800 annual patient admissions. Institutional Review Board approval was obtained from Columbia University Medical Center and Weill Cornell Medical College with a waiver of informed consent.

Study subjects and case definitions

The cohort was defined as all patients admitted to the study ICUs during the study period. Case subjects were defined as patients hospitalized in the ICU with health care-associated bloodstream infections (BSIs), pneumonia (PNA), or urinary tract infections (UTIs) caused by XDR-*Acinetobacter* spp, *Klebsiella pneumoniae*, or *Pseudomonas aeruginosa* (defined below). Control subjects were defined as patients hospitalized in the ICU with HAIs caused by non-XDR *Acinetobacter* spp, *K pneumoniae*, or *P aeruginosa*. HAIs were diagnosed using the Centers for Disease Control and Prevention's National Hospital Safety Network definitions[5] but modified to include antimicrobial treatment. When feasible, case and control subjects were matched (1:2) by the following matching hierarchy: campus (Columbia or Cornell), type of ICU (medical or surgical), type of infection (BSI, PNA, or UTI), date of culture, and pathogen (*Acinetobacter* spp, *K pneumoniae*, or *P aeruginosa*). Patients were excluded if their infections developed <48 hours after hospital admission, were a non-study type of infection, eg, skin and soft tissue infection, or were caused by a non-study pathogen.

XDR-GNB were the species described above, susceptible to ≤1 antimicrobial agent or only susceptible to imipenem and meropenem as determined by commercial broth microdilution susceptibility panels (described below). Non-XDR-GNB were susceptible to ≥2 antimicrobial agents. Susceptibility to tigecycline and polymyxin B were not included in the definitions of XDR- and non-XDR-GNB because these agents were not consistently tested at the study sites. Minimum inhibitory concentrations (MICs) were interpreted according to the Clinical and Laboratory Standards Institute break points in effect during the study period.[6-8]

Potential subjects were identified prospectively using EpiPortal, a Web-based surveillance system developed by the NYP Department of Infection Prevention and Control and Department of Information Technology and Columbia University Department of Biomedical Informatics.[9] EpiPortal integrates data from different electronic systems (eg, microbiology laboratories, pharmacy, medical records) to identify patients with epidemiologically significant organisms including multidrug-resistant pathogens. The electronic medical record of each potential subject was reviewed by a study physician to confirm case or control status and to determine the presence of comorbid conditions, antibiotic exposures, and medical device use (central venous catheter, mechanical ventilation, and/or urinary catheter). Demographic and microbiologic data were also obtained from the electronic medical record.

At the Columbia campus, blood culture samples from adults were inoculated into BD Bactec Plus Aerobic/F and Bactec Lytic/10 Anaerobic/F bottles, and pediatric samples were inoculated into Bactec Peds Plus/F bottles (Becton Dickinson, Franklin Lakes, NJ). At the Cornell campus, blood culture samples obtained from adults and children were inoculated into BactT Alert bottles (bioMérieux, Durham, NC). Respiratory and urine samples were plated onto MacConkey agar at both study sites. During the study period, the clinical microbiology laboratories used the Vitek 2 system (bioMérieux) as the primary method of antibiotic susceptibility testing (AST). The laboratory on the Columbia campus used the Vitek 2 AST GN09 prior to May 2009 and afterwards used GN35. The laboratory on the Cornell campus used Vitek 2 AST GN13 prior to January 2009 and afterwards used GN28 for *Klebsiella* and *Acinetobacter* spp and GN31 for *P aeruginosa*. Both laboratories performed Etests (bioMérieux) to determine susceptibility to polymyxin B and tigecycline for XDR strains if requested, and, at Cornell, Etests for tigecycline were regularly performed after January 2009.

Risk factors for HAIs and predictors of mortality

Risk factors evaluated for HAIs caused by XDR-GNB versus non-XDR-GNB included age, sex, race, and ethnicity; days of ICU and hospital stay prior to infection; comorbid conditions (defined below); exposure to antibiotics administered during hospitalization in the 30 days prior to infection; and use of medical devices in the 7 days prior to infection. Comorbid conditions were defined using APACHE II/III classification.[10] Briefly, liver disease was defined as biopsy-proven cirrhosis or portal hypertension; respiratory disease was defined as a chronic process resulting in severe exercise restriction; cardiovascular disease was defined as symptoms of cardiac insufficiency at rest; renal impairment was defined as the use of chronic dialysis; and immunocompromised state was defined as conditions that increased susceptibility to infection (eg, leukemia/lymphoma, metastatic cancer) or receipt of immunosuppressant medications (eg, chemotherapy, high dose steroids). Potential predictors of mortality were infection with an XDR-GNB, age, sex, comorbid conditions, type of ICU, duration of ICU stay prior to infection, pathogen, type of infection, and time to effective therapy (defined below).

Outcomes

The onset of HAIs was defined as the first day of positive culture(s). Several outcomes related to antibiotic treatment were compared among case versus control subjects. These included (1) duration of therapy (calendar days) with ≥1 antibiotic(s) with GNB activity administered following HAI diagnosis; (2) the number of