Antimicrobial-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* From Patients With Hospital-acquired or Ventilator-associated Pneumonia in Vietnam

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ABSTRACT

Purpose: Multidrug-resistant bacterial pathogens are becoming a significant problem worldwide. *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are problematic multidrug-resistant pathogens. This multicenter study in Vietnam determined the level of resistance to antimicrobial agents used to treat *A baumannii* and *P aeruginosa* infections in this country.

Methods: Five medical centers in Vietnam provided 529 *P aeruginosa* and 971 *Acinetobacter* species (904 *A baumannii*) isolates from patients with hospital-acquired or ventilator-associated pneumonia from 2012 to 2014. A central laboratory verified identification of the isolates and performed susceptibility testing using Clinical and Laboratory Standards Institute methods.

Findings: Resistance to cephalosporins, β-lactam/β-lactamase inhibitors, carbapenems, and fluoroquinolones was >90% against *A baumannii*. Aminoglycosides had only slightly better activity, with amikacin resistance >80%. Only colistin (MIC_{90}, ≤0.25 mg/L) and tigecycline (MIC_{90}, 4 mg/L) had appreciable activity against *A baumannii*. Similar activity was observed among the β-lactams tested against *P aeruginosa*. Cefepime demonstrated the highest activity (60.1% susceptible), which was similar to doripenem (58.6% susceptible), the most active carbapenem tested. Amikacin was the most active aminoglycoside tested against *P aeruginosa*, with susceptibility of 81.7% compared with tobramycin (58.0%) and gentamicin (56.5%). Fluoroquinolones had limited activity against *P aeruginosa* with susceptibility to ciprofloxacin (55.0%). All *P aeruginosa* isolates had colistin MIC values ≤2 mg/L.

Implications: The data from this 3-year longitudinal study in Vietnam demonstrate that 2 of the most common nonfermentative gram-negative pathogens associated with hospital-acquired and ventilator-associated pneumonia are significantly resistant to most of the available treatment options and require combination therapies unless new antimicrobial agents become available. (*Clin Ther.* 2016;38:2098–2105) © 2016 Published by Elsevier HS Journals, Inc.

Key words: antimicrobial resistance, carbapenems, surveillance, Vietnam.

INTRODUCTION

The dissemination of drug-resistant bacterial pathogens is becoming prevalent and is a major concern for health care providers in the hospital and community.[1] A recent report suggests that multidrug-resistant (MDR) and extensively drug-resistant pathogen infections could cause the deaths of 10 million people each year worldwide by 2050.[2] This mortality rate could surpass that due to cancer at a cost estimated at $100 trillion. Developed countries have been forced to provide

Accepted for publication July 29, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.07.172
0149-2918/$ - see front matter

significant resources to abate this problem. Developing countries do not have these resources available.

In the United States, the current government administration announced a proposal to nearly double the amount of funding in the 2016 budget to prevent the spread of antibiotic-resistant microbial pathogens.[3] This funding amounts to $1.2 billion for biomedical research and public health surveillance against antibiotic-resistant bacteria. Similar measures are being taken by the government in the United Kingdom, which released a recent document entitled "Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations." This document is the first paper by the Review on Antimicrobial Resistance.[4] It illustrates that if antimicrobial resistance continues to be ignored, profound health and macroeconomic consequences worldwide are possible, especially in emerging economies.

Hospital formulary committees evaluate antimicrobial agents used in their local settings and the epidemiology of their local hospital bacterial flora.[5,6] Monitoring antimicrobial resistance patterns among human pathogens, including those isolated from a particular source of infection, is essential to guide effective empiric therapy.[7,8]

Pseudomonas aeruginosa and *Acinetobacter baumannii* are common bacterial pathogens isolated from patients with hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).[6] MDR or extreme drug-resistant infections cause significant morbidity and mortality, and they require extensive resources from a fiscal and patient care perspective. The resistance mechanisms associated with both species can be complex and limit therapeutic choices.[9,10] β-lactams (including those with a β-lactamase inhibitor), carbapenems, fluoroquinolones, aminoglycosides, and colistin are currently the only effective drugs available and are often used in combination therapy. Increasing resistance to each of these drug classes has been a concern for both *P aeruginosa* and *A baumannii*.[11,12]

Limited information on antimicrobial resistance is available in countries with emerging economies, including Vietnam.[13,14] This problem is exacerbated by lack of controlled prescribing practices and individuals taking antimicrobial agents without consultation of a physician.[15–17] The present antimicrobial surveillance initiative was designed to focus on the susceptibility of 2 common MDR or extreme drug-resistant nonfermentative species isolated from patients with HAP or VAP in Vietnam. The study monitored the susceptibility patterns of *P aeruginosa* and *Acinetobacter* species to determine antimicrobial susceptibility of agents used to treat HAP and VAP infections over a 3-year period in 5 Vietnamese hospitals.

PATIENTS AND METHODS

Five centers in Vietnam participated in this study: Nguyen Tri Phuong Hospital (Ho Chi Minh City), Nhan Dan Gia Dinh Hospital (Hachiman City), National Hospital of Tropical Diseases (Hanoi), Cho Ray Hospital (Ho Chi Minh City), and Bach Mai Hospital (Hanoi). This was an in vitro study only and did not include patients or animals; therefore, informed consent was not needed.

Each site collected consecutive clinical isolates of *P aeruginosa* or *A baumannii* considered the causative pathogen from patients diagnosed by clinician judgment as having HAP or VAP each calendar year (2012–2014). Isolates were cultured from quantitative or semi-quantitative lower respiratory tract specimens (endotracheal aspirates, bronchoalveolar lavage, and protected brush specimens collected with or without a bronchoscope). Only the first isolate of each species per patient was accepted. HAP was defined as pneumonia developing >48 hours after admission to the hospital that was not incubating at time of admission. VAP was defined as pneumonia developing >48 to 72 hours after endotracheal intubation.

This collection consisted of 1500 isolates comprising 529 *P aeruginosa* isolates, 904 *A baumannii* isolates, and 67 other *Acinetobacter* species (6 species) isolates. All isolates were transferred to a central laboratory (International Health Management Associates, Inc, Schaumburg, Illinois). The central laboratory confirmed isolate identification to the species level by using MALDI-TOF (Bruker Daltronics, Bremen, Germany). MICs were determined by using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method using reagent grade antimicrobial agents obtained commercially or by the appropriate licensed manufacturing company.[18] Susceptibility for antimicrobial agents was interpreted and validated by using concurrent testing of quality control strains recommended by the CLSI.[19]

RESULTS

The in vitro susceptibility and antimicrobial activity of cephalosporins, carbapenems, β-lactam/β-lactamase inhibitors, aminoglycosides, fluoroquinolones, colistin, and tigecycline against *P aeruginosa* and *Acinetobacter* species are shown in the Table.