Diagnostic Microbiology and Infectious Disease 78 (2014) 457–461

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Clinical Outcomes

Risk factors for hospital-acquired pneumonia caused by carbapenem-resistant Gram-negative bacteria in critically ill patients: a multicenter study in Korea

Tark Kim [a,1], Yong Pil Chong [a,b,1], Seong Yeon Park [c], Min-Hyok Jeon [d], Eun Joo Choo [e], Jin-Won Chung [f], Hyun Kyung Lee [g], Chisook Moon [h], Dong-Min Kim [i], Kyong Ran Peck [j], Yang Soo Kim [a,b,*]

[a] Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[b] Center for Antimicrobial Resistance and Microbial Genetics, University of Ulsan, Seoul, Republic of Korea
[c] Division of Infectious Diseases, Department of Internal Medicine, Dongguk University Ilsan Hospital, Seoul, Republic of Korea
[d] Division of Infectious Diseases, Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Cheonan, Republic of Korea
[e] Division of Infectious Diseases, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea
[f] Division of Infectious Diseases, Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Republic of Korea
[g] Division of Respiratory Medicine, Department of Internal Medicine, Inje University Busan Paik Hospital, Busan, Republic of Korea
[h] Division of Infectious Diseases, Department of Internal Medicine, Inje University Busan Paik Hospital, Busan, Republic of Korea
[i] Division of Infectious Diseases, Department of Internal Medicine, Chosun University Hospital, Gwangju, Republic of Korea
[j] Division of Infectious Diseases, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 25 June 2013
Received in revised form 16 August 2013
Accepted 23 August 2013
Available online 23 January 2014

Keywords:
Risk factor
Hospital-acquired pneumonia
Carbapenem-resistant Gram-negative bacteria

ABSTRACT

We performed a case–control study to identify risk factors of carbapenem-resistant Gram-negative bacteria (CRGNB) as an increasing cause of hospital-acquired pneumonia (HAP). The study included critically ill adult patients with HAP whose microbial etiology was identified at eight tertiary centers in Korea between June 2008 and December 2009. Eighty two patients with 86 isolates of CRGNB (62 *Acinetobacter baumannii*, 14 *Pseudomonas aeruginosa*, and 10 *Stenotrophomonas maltophilia*) were included in the case group, and 122 patients with carbapenem-susceptible Gram-negative bacteria were included in the control group. Diabetes mellitus (adjusted odds ratio [aOR] 2.82, 95% confidence interval [95% CI] 1.25–6.38), radiologic score ≥5 (aOR 4.56, 95% CI 2.36–8.81), prior fluoroquinolone (aOR 2.39. 95% CI = 1.07–5.35), or carbapenem usage (aOR 2.82, 95% CI 1.75–17.83) were found to be independent risk factors. Fluoroquinolone and carbapenem should be cautiously used to avoid HAP caused by CRGNB.

1. Introduction

Hospital-acquired pneumonia (HAP) is a major nosocomial infection resulting in increased morbidity, mortality, and medical costs (Giske et al., 2008). Administration of appropriate antibiotics is very important to improve the outcome of HAP (Alvarez-Lerma, 1996; Iregui et al., 2002), and it should be based on epidemiologic data of the causative microbial pathogens (ATS, 2005). Although there are geographic differences, data from previous epidemiologic studies on HAP patients suggests that multidrug-resistant organisms are on the rise (Jones, 2010). In Asia, especially, carbapenem-resistant microbial pathogens, such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, are major pathogens of HAP (Chung et al., 2011). The Korean Nosocomial Infections Surveillance System, carried out between July 2009 and June 2010, showed an increase in the incidence of imipenem-resistant *A. baumannii* infection from 43.6% to 82.5% since July 2006 (Kwak et al., 2011). Therefore, to prevent inappropriate empirical therapy and overuse of colistin as a last weapon against carbapenem-resistant organisms, it is important to identify the risk factors for carbepenem-resistant bacterial infection in HAP.

Several studies have addressed the identification of risk factors for the isolation of carbapenem-resistant pathogens in hospitalized patients (D'Agata et al., 2006; Garnacho-Montero et al., 2005; Leroy et al., 2005; Lodise et al., 2007; Mentzelopoulos et al., 2007; Trouillet et al., 1998; Young et al., 2007). However, the results varied due to the different study populations and definitions of multidrug-resistant pathogens. Most of these studies dealt with patients with a specific pathogen, such as *A. baumannii* or *P. aeruginosa*, and the risk factors for pneumonia caused by multidrug-resistant pathogens were investigated less than those for bacteremia. To date, no studies have been performed to compare patients with HAP caused by carbapenem-resistant Gram-negative bacteria (CRGNB) to those who developed HAP caused by carbapenem-susceptible Gram-negative bacteria (CSGNB).

For this reason, we conducted this multicenter study to identify the risk factors for HAP caused by CRGNB.

* Corresponding author. Tel.: +82-2-3010-3303; fax: +82-2-3010-6970.
E-mail address: yskim@amc.seoul.kr (Y.S. Kim).
[1] Both authors equally contributed to this work.

0732-8893/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.diagmicrobio.2013.08.011

2. Materials and methods

2.1. Study population and design

This retrospective multicenter study was conducted at 8 tertiary teaching centers in Korea. We searched the medical records of patients admitted to the intensive care unit at each center between June 2008 and Dec 2009. Patients >16 years old who met the following criteria were included: (1) new or persistent pulmonary infiltrate; (2) 2 or more symptoms and signs including body temperature >38.5 °C or <35.5 °C, white leukocyte counts >12000/mm^3 or <4000/mm^3, and purulent sputum; and (3) microbial organisms isolated by methods including quantitative culture ($\geq 10^4$ cfu/mL) of bronchoalveolar lavage (BAL) specimen, semiquantitative culture (moderate or heavy growth) of bronchoscopic aspirate or BAL specimen, quantitative culture ($\geq 10^5$ cfu/mL) of endotracheal aspirate, and semiquantitative culture (moderate or heavy growth) of endotracheal aspirate with white blood cells (WBC) >25/high power field (HPF) on Gram stain, or adequate sputum with WBC >25/HPF and epithelial cell ≤10 on Gram stain. HAP was defined as pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission. Ventilator-associated pneumonia (VAP) referred to pneumonia arising more than 48 hours after endotracheal intubation. Bacterial identification was performed using standard methods. Susceptibility testing was done using the microdilution method (MicroScan system; Baxter Health Care, West Sacramento, CA, USA), and results were interpreted according to the National Committee for Clinical Laboratory Standards guidelines published in 2008 (CLSI, 2008). Meropenem or imipenem resistance was defined as a minimal inhibitory concentration of 16 μg/ml or above. CRGNB were defined as Gram-negative bacteria resistant to either meropenem or imipenem and *Stenotrophomonas maltophilia* that is known to have intrinsic resistance to carbapenem (Denton and Kerr, 1998).

Patients with CRGNB were categorized in the case group, while patients with only CSGNB were categorized in the control group. Patients with both CRGNB and CSGNB were categorized in the case group. Patients with HAP caused by only Gram-positive bacteria, such as *Staphylococcus aureus* and *Streptococcus pneumoniae*, were excluded from the analysis. To identify risk factors associated with HAP caused by CRGNB, clinical variables of the case group were compared to those of the control group. Additionally, by comparing clinical variables between patients with and without in-hospital mortality, risk factors associated with in-hospital mortality were also evaluated.

2.2. Data collection

Patients' demographic data and comorbidity (congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease, liver cirrhosis on Child B or C classification, hematologic malignancy, solid tumor, interstitial lung disease, alcoholism, end-stage renal disease on dialysis, neurologic diseases, and trauma) were collected. Comorbidities were diagnosed by laboratory findings, pathologic diagnosis, and clinician's judgment during admission. Comorbidities which had been previously diagnosed were searched by reviewing past medical. To estimate the severity of comorbidity, the McCabe and Jackson classification was used (McCabe and Jackson, 1962): nonfatal disease (diabetes, genitourinary, gastrointestinal or obstetrical conditions), ultimately fatal disease (diseases estimated to become fatal within 4 years, e.g., aplastic anemia, chronic leukemia, myeloma, lymphoma, metastatic carcinoma, systemic lupus erythematous with nephritis, liver cirrhosis with hepatic coma or bleeding varices, chronic renal disease, or rapidly fatal disease (acute leukemia, blastic relapse of chronic leukemia). HAP occurring within the first 5 days of admission was considered early onset. We searched whether a patient was on mechanical ventilation, and received antibiotics such as broad-spectrum cephalosporin, extended-spectrum penicillin/β-lactamase inhibitor, fluoroquinolone, aminoglycoside, and carbapenem for 48 hours or more within 15 days of HAP onset. The initial severity of HAP was estimated using the Acute Physiology and Chronic health Evaluation (APACHE) II score (Knaus et al., 1985). A radiologic score was also assessed as previously described (Nseir et al., 2008). Anterior-posterior chest X-rays were divided into four zones using a horizontal line originating from the hilus. Each zone was graded and summed up as follows: 0, normal; 1, interstitial pulmonary infiltrates; 2, fluffy alveolar infiltrates; 3, dense alveolar infiltrates.

2.3. Statistical analysis

Statistical analyses were performed with SPSS for Windows (version 18.0; SPSS Inc, Chicago, IL, USA). Continuous variables were compared using the Mann–Whitney *U* test or Student's *t* test, as appropriate. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. A binary logistic regression was used to identify variables significantly associated with HAP caused by CRGNB. The variables found to be statistically significant at a 10% level in the univariate analysis were included in the multivariate analysis. A stepwise forward entry was selected for multivariate analysis. All significance testing was 2 tailed, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Study population

During the study period, 372 bacterial pathogens were isolated from 320 adult patients with HAP. Out of these patients, 51 had a polymicrobial infection (2 different pathogens isolated in 50 patients, and 3 different pathogens isolated in one patient). *S. aureus* (130,

Table 1
Comparison of clinical characteristics of hospital-acquired pneumonia caused by carbapenem-resistant and carbapenem-susceptible Gram-negative bacteria.

Clinical characteristic	Carbapenem-resistant (n = 82)	Carbapenem-susceptible (n = 122)	*P* value
Demographic			
Age, median yrs (IQR)	67 (59–73)	69 (56–77)	0.36
Gender, male	49 (59.8)	84 (68.9)	0.18
Underlying medical condition			
Congestive heart failure	7 (8.5)	10 (8.2)	1.00
Diabetes mellitus	22 (26.8)	17 (13.9)	0.029
COPD	4 (4.9)	2 (1.6)	0.22
Liver cirrhosis, Child B or C	1 (1.2)	4 (3.3)	0.65
Hematologic malignancy	5 (6.1)	4 (3.3)	0.49
Solid tumor	13 (15.9)	12 (10.7)	0.29
Interstitial lung diseases	4 (4.9)	3 (2.5)	0.44
Alcoholism	2 (2.4)	6 (4.9)	0.48
ESRD on dialysis	6 (7.3)	6 (4.9)	0.55
Neurologic diseases	26 (31.7)	59 (48.4)	0.021
Trauma	6 (7.3)	10 (8.2)	1.00
MaCabe and Jackson Classification			
Rapidly or ultimately fatal	38 (48.8)	40 (32.8)	0.08
Early onset	8 (9.8)	18 (14.8)	0.39
Ventilator-associated pneumonia	54 (65.9)	60 (49.2)	0.022
Prior antibiotics usage			
Broad-spectrum cephalosporin	35 (42.7)	48 (39.3)	0.67
Extended-spectrum penicillin/β-lactamase inhibitor	29 (35.4)	32 (26.2)	0.21
Fluoroquinolone	27 (32.9)	15 (12.3)	0.001
Aminoglycoside	17 (20.7)	17 (13.9)	0.25
Carbapenem	18 (22.0)	5 (4.1)	<0.001
Initial severity			
APACHE II, median (IQR)	26 (21–31)	23 (17–28)	0.016
Radiologic score, median (IQR)	7 (4–9)	4 (3–6)	<0.001
In-hospital mortality	50 (61.0)	47 (38.8)	0.003

IQR = interquartile range; COPD = chronic obstructive pulmonary disease; ESRD, end-stage renal disease.