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ARTICLE

Clinical outcomes and risk factors of community-acquired pneumonia caused by gram-negative bacilli

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Abstract To identify specific risk factors and clinical outcomes of community-acquired pneumonia (CAP) caused by gram-negative bacilli (GNB), we compared the clinical features and outcomes of patients with CAP due to GNB with those of patients with non-GNB pneumonia. We performed a prospective observational study of 912 cases of adult CAP in Asian countries from January 2002 to December 2004. Systemic laboratory evaluation for determining the etiology and clinical evaluation were performed. Of 912 cases with CAP, 93 (10.1%) cases were caused by GNB: 59 with *K. pneumoniae*, 25 *P. aeruginosa*, 7 *Enterobacter* species, 1 *Acinetobacter baumannii*, and 1 *Serratia marcescens*. CAP caused by GNB was more frequently associated with septic shock, malignancy, cardiovascular diseases, smoking, hyponatremia, and dyspnea, according to multivariate analysis ($P<0.05$). Overall 30-day mortality rate was 7.3% (65/885). Mortality was significantly higher in the GNB group than in the non-GNB group [18.3% (17/93) vs. 6.1% (48/792); $P<0.001$]. GNB as a causative microorganism was found to be one of the independent risk factors for mortality (adjusted OR=2.63, 95% CI 1.02–6.78, $P=0.046$) with nursing home residence, mechanical ventilation, cardiovascular disease, respiratory rate >30/min, and hyponatremia (all $P<0.05$). GNB was not only a frequent etiology of severe CAP but also an independent risk factor for mortality. Data suggest that an initial empirical antimicrobial coverage of GNB including *P. aeruginosa* should be seriously considered in cases of severe pneumonia, especially in patients with underlying malignancy, underlying cardiovascular diseases, smoking, septic shock, and hyponatremia.

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Introduction

Community-acquired pneumonia (CAP) still remains one of the most important diseases with significant morbidity and mortality [1, 2]. Selection of appropriate antimicrobial regimens for empirical therapy of CAP is directly associated with clinical outcome of pneumonia [3, 4]. Gram-negative bacilli (GNB) could be a frequent cause of inappropriate treatment with adverse prognostic potential because these pathogens are infrequent causes of CAP and also tend to be resistant to multiple antibiotics that are selected for the treatment of CAP [5–10]. Furthermore, pneumonia due to GNB is more common in immunocompromised patients. Despite the clinical importance of CAP caused by GNB, however, there have been relatively few data about the epidemiology and clinical outcomes of GNB pneumonia, especially in Asian countries [11]. Recently, the Asian Network for Surveillance of Resistant Pathogens (ANSORP) conducted a prospective surveillance study of

CAP in Asian countries [12]. From this study, we have analyzed the data regarding GNB pneumonia to identify the specific risk factors for GNB pneumonia and the clinical impact of GNB on final outcomes of CAP.

Patients and methods

Study population

ANSORP conducted a prospective surveillance study from January 2002 to December 2004 in 14 tertiary care hospitals in eight Asian countries: Korea (Samsung Medical Center, Kangbuk Samsung Hospital, Seoul Veterans Hospital, Seoul; Gyungbook National University, Daegu; Chungnam National University, Daejeon; Chonnam National University, Gwangju), China (Chao Yang Hospital, Beijing; Rui Jin Hospital, Shanghai), Taiwan (Chang Gung Memorial Hospital and National Taiwan University, Taipei), Hong Kong (Princess Margaret Hospital, Hong Kong), India (Christian Medical College, Vellore), Singapore (Singapore General Hospital, Singapore), Vietnam (University of Medicine and Pharmacy, HCMC), and the Philippines (Research Institute of Tropical Medicine, Manila).

All adult patients who fulfilled the criteria of clinical and radiological diagnosis of CAP were enrolled in the study. CAP was defined as follows: (1) new or progressive infiltrate (s), consolidation or pleural effusion consistent with pneumonia in chest radiography performed within 48 h prior to enrollment, (2) fever or a history of fever (defined as an oral temperature >38°C), and (3) at least two respiratory signs and symptoms (new or increased cough, purulent sputum or a change in sputum characteristics, auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation, dyspnea or tarchypnea, peripheral white blood cell count >10,000 cells/mm^3 or >15% immature neutrophils or leukopenia with a total WBC count of <4,500 cells/mm^3, hypoxemia with a PO_2 <60 mmHg while the patient is breathing room air). Patients younger than 15 years old, patients who had been hospitalized for more than 72 h or who had been discharged from an acute care hospital within 10 days, patients who had organ transplantation within 6 months, SARS, or known HIV infection were excluded from the study.

Study design and data collection

We compared data from patients with CAP due to GNB with CAP caused by other pathogens. All enrolled patients were evaluated with regard to clinical, radiological, and microbiological findings. The presence of the following comorbid conditions was determined: bronchopulmonary disease (e.g., asthma, chronic obstructive pulmonary disease, or interstitial lung disease), cardiovascular disease (e.g., congestive heart failure, coronary artery disease, or valvular heart disease), malignancy, neurological disease, renal disease, and immunosuppression. Based on these findings, a pneumonia severity index (PSI) was calculated [13]. For this study, specific antibiotic regimens were not recommended. Treatment regimens were chosen by the patients' physicians without any guidelines or intervention from the study protocol or study investigators. Uses of antimicrobial agents in all centers were recorded, and follow-up evaluation was done for clinical, radiological, and microbiological responses to antimicrobial therapy. The clinical outcome was measured by the 30-day mortality rate.

The initial antimicrobial therapy was considered "appropriate" if the treatment regimen included at least one antibiotic active in vitro against identified pathogens, and if the dosage and route of administration conformed to current medical standards. We considered antimicrobial therapy "inappropriate" if the drugs used did not have in vitro activity against the isolated strain or if the patient did not receive any antimicrobial therapy initially.

Microbiological evaluation

At the time of enrollment, sputum cultures, blood cultures (if feasible), and serologic tests for atypical pathogens were performed. All microbiological evaluations were performed before initiation of antimicrobial treatment. All sputum specimens and other samples of respiratory secretions were gram-stained and examined microscopically for the presence of WBC, epithelial cells, and bacteria. Purulence was measured by microscopy and was acceptable if > 25 WBC and < 10 squamous epithelial cells per low-power field were found. Results from the sputum cultures were only considered significant if the gram-stains criteria above were satisfied.

Statistical analysis

The Student's *t*-test was used to compare continuous variables, and χ^2 or Fisher's exact test was used to compare categorical variables. In identifying the independent risk factors for mortality, a stepwise conditional logistic regression analysis was used to control for the effects of confounding variables. All *P* values were two-tailed, and *P* values < 0.05 were considered statistically significant.

Results

Study population

Out of 912 cases with CAP, a total of 390 bacterial pathogens were isolated from 349 patients [12]. Of 390

isolates, *S. pneumoniae* (29.2%) was the most frequent isolate, followed by *K. pneumoniae* (15.4%), *H. influenzae* (15.1%), *P. aeruginosa* (6.7%), *S. aureus* (4.9%), *M. tuberculosis* (3.3%), *M. catarrhalis* (3.1%), and *E. cloacae* (2.6%). Of 912 cases with CAP, 93 cases (10.1%) were caused by GNB: 59 with *K. pneumoniae*, 25 *P. aeruginosa*, 7 *Enterobacter* species, 1 *Acinetobacter baumannii*, and 1 *Serratia marcescens*. The detailed characteristics of study population have been described in our previous report [12].

Clinical features of GNB pneumonia

We compared demographic data of patients with CAP due to GNB with those of patients with CAP due to other etiologies (Table 1). As for the demographic and clinical characteristics of the study population, bronchopulmonary diseases and cardiovascular diseases were found more frequently among patients with CAP due to GNB [36/93 (39%) vs. 250/819 (31%), P=0.11; 26/93 (28%) vs. 164/819 (20%), P=0.074, respectively], but the comparison of both groups was not statistically significant. Smoking history was significantly more frequent in patients with GNB [34/93 (37%) vs. 204/819 (25%), P=0.015].

In addition, with regard to the initial clinical manifestation and laboratory findings (Table 2), patients with CAP due to GNB were more likely to present with dyspnea, chest pain, and altered mentality. Tachypnea (respiratory rate ≥ 30/min) and septic shock were also more common in CAP due to GNB. Azotemia (BUN ≥ 30 mg/dL), hypoxemia, multilobar involvement, and hyponatremia (serum sodium ≤ 130 mEq/L) were present significantly more often on admission in patients with GNB. Patients with GNB pneumonia required mechanical ventilation more often. When we compared data of patients with GNB with those with pathogens other than GNB in microbiologically confirmed cases, purulent sputum, dyspnea, chest pain, altered mentality, hypotension, and azotemia were more frequent in GNB group (all P<0.05).

A multivariate analysis showed that GNB cases were more frequently associated with septic shock, malignancy, cardiovascular diseases, smoking, hyponatremia, and dyspnea than other pathogens (all P<0.05) (Table 3). In addition, by multivariate analysis including only microbiologically confirmed cases, presentation with septic shock, dyspnea, and azotemia were found to be independent predictors for GNB pneumonia (all P<0.05).

Clinical outcomes and risk factors for mortality

We evaluated 885 cases of CAP for outcome analysis. Overall 30-day mortality rate was 7.3% (65/885). The mortality of CAP was significantly higher in GNB group than in non-GNB group [18.3% (17/93) vs. 6.1% (48/792), P<0.001]. In the univariate analysis, the factors associated with 30-day mortality were as follows: old age, nursing home residence, malignancy, cardiovascular diseases, renal diseases, prior hospitalization, altered mentality, respiratory rate >30/min, BP <90 mmHg, pulse rate >110/min,

Table 1 Demographic and clinical characteristics of patients with community-acquired pneumonia (CAP) due to gram-negative bacilli compared with CAP patients with other etiologies

	Gram-negative bacilli (n=93)	Others (n=819)	P
Age (years, mean ± SD, range)	61±12 (20–90)	57±14 (16–94)	0.009
Old age (> 65 years old)	24 (25.8)	156 (19.0)	0.121
Male	60 (64.5)	511 (62.4)	0.695
Underlying diseases			
Bronchopulmonary disorder	36 (38.7)	250 (30.5)	0.107
Cardiovascular disorder	26 (28.0)	164 (20.0)	0.074
Neoplastic disorder	16 (17.2)	96 (11.7)	0.127
Neurological disorder	12 (12.9)	66 (8.1)	0.113
Liver disorder	5 (5.4)	37 (4.5)	0.608
Renal disorder	4 (4.3)	35 (4.3)	1.000
Comorbid conditions			
Smoking	34 (36.6)	204 (24.9)	0.015
High alcohol intake	10 (10.8)	50 (6.1)	0.087
Residence in nursing home	4 (4.3)	25 (3.1)	0.527
Recent hospitalization	9 (9.7)	60 (7.3)	0.416
Prior use of antimicrobial agent	21/80 (26.3)	209/680 (30.7)	0.409
Neutropenia	3 (3.2)	30 (3.7)	0.831
Use of corticosteroid	2 (2.2)	16 (2.0)	0.705

Unless otherwise indicated, data represent patient numbers (percentage)
SD Standard deviation

Table 2 Clinical manifestations and laboratory findings at initial presentation in patients with community-acquired pneumonia due to gram-negative bacilli compared to those with other etiologies

Findings	Gram-negative bacilli (n=93)	Others (n=819)	P
Symptoms			
Cough	78/84 (92.9)	665/717 (92.7)	0.971
Purulent sputum	78/83 (94.0)	606/693 (87.4)	0.082
Dyspnea	62/78 (79.5)	417/688 (60.6)	0.001
Chest pain	39/80 (48.8)	225/669 (33.6)	0.007
Altered mentality	19/84 (22.6)	67/717 (9.3)	<0.001
Signs			
Respiratory rate ≥ 30/min	15/93 (16.1)	74/819 (9.0)	0.029
Heart rate ≥ 125/min	7/93 (7.5)	59/819 (7.2)	0.909
Temperature ≥ 40°C or < 35°C	4/93 (4.3)	48/819 (5.9)	0.539
Systolic blood pressure < 90 mmHg	8/93 (8.6)	21/819 (2.6)	0.006
Laboratory findings			
WBC ≥ 10,000/mm^3	67/92 (72.8)	521/790 (65.9)	0.185
BUN ≥ 30 mg/dL	24/84 (28.6)	140/763 (18.3)	0.024
PaO_2 < 60 mmHg or SaO_2 < 90%	20/89 (22.5)	102/742 (13.7)	0.028
Hct < 30%	16/91 (17.6)	81/788 (10.3)	0.035
Serum sodium < 130 mEq/L	13/85 (15.3)	66/771 (8.6)	0.042
Glucose ≥ 250 mg/dL	12/82 (14.6)	63/758 (8.3)	0.056
Radiologic findings			
Lobar pneumonia	38/90 (42.2)	342/771 (44.4)	
Bronchopneumonia	35/90 (38.9)	361/771 (46.8)	
Interstitial pneumonia	17/90 (18.9)	68/771 (8.8)	
Multilobar involvement	41/84 (48.8)	250/732 (34.2)	0.008
Pleural effusion	19/91 (20.9)	112/781 (14.3)	0.099
Pneumonia severity index			
I	22/93 (23.7)	179/793 (22.6)	<0.001
II	15/93 (16.1)	239/793 (30.1)	
III	13/93 (14.0)	156/793 (19.7)	
IV	24/93 (25.8)	167/793 (21.1)	
V	19/93 (20.4)	52/793 (6.6)	
ICU admission	10/93 (10.8)	58/793 (7.3)	0.239
Mechanical ventilation	11/84 (13.1)	49/705 (7.0)	0.045

Exact numbers are given for each variable; information was not available for all patients. Data represent patient numbers (percentage)

leukocytosis, azotemia, hypoxemia, hyponatremia, high glucose level, low hematocrit level, multilobar involvement, pleural effusion, and mechanical ventilation. In the multivariate analysis, GNB as causative microorganism was found to be one of the significant factors associated with mortality (adjusted OR=2.63, 95% CI=1.02–6.78, P=0.046). Nursing home residence, mechanical ventilation, cardiovascular diseases, respiratory rate >30/min, and hyponatremia were also found to be independent risk factors for mortality (all P<0.05).

When we evaluated the appropriateness of antimicrobial therapy in cases that could be evaluated (n=318), initial antimicrobial therapy was inappropriate in 45.1% (32/71) of GNB group and in 13.4% (33/247) of non-GNB group (P<0.001). There was no significant difference in 30-day mortality between initial appropriate therapy group and the inappropriate therapy group [9.1% (23/253) vs. 10.8% (7/65), P=0.68].

Discussion

From this multinational surveillance study of CAP in Asian countries, we identified several risk factors for GNB infection including underlying malignancy or cardiovascular diseases, and smoking. However, severe underlying bronchopulmonary disease, alcoholism, and previous antibiotic therapy [1, 5, 7], which have been reported to be associated with CAP due to *Enterobacteriaceae* and *P. aeruginosa,* were not found to be associated with GNB pneumonia in our study. GNB, especially *P. aeruginosa*, was associated with severe pneumonia [8, 9, 14]. In our study, presentation with septic shock and initial hyponatremia was one of the predictive factors for GNB pneumonia, as well as one of the risk factors for mortality. We assessed the relationship between etiological pathogens and final clinical outcome of CAP. Data confirmed that GNB caused adverse clinical outcome in patients with CAP compared with non-GNB pathogens. Mortality in patients with GNB was 18%, compared with 6% in the non-GNB group. GNB was found to be an independent risk factor for mortality in the multivariate analysis. These findings are consistent with previous reports [5, 8, 9].

Based on our data about independent risk factors for GNB pneumonia, initial selection of empirical antimicrobial agents should be effective against GNB if patients have septic shock, underlying malignancy, underlying cardiovas-

Table 3 Independent risk factors for gram-negative bacilli as causes of community-acquired pneumonia by multivariate analysis[a]

Variables	Adjusted OR (95% CI)	P value
Presentation with septic shock	4.10 (1.64–10.23)	0.002
Malignancy	1.91 (1.02–3.57)	0.043
Cardiovascular diseases	1.78 (1.07–2.96)	0.026
Smoking	1.72 (1.06–2.81)	0.030
Hyponatremia	1.23 (1.09–1.37)	<0.001
Dyspnea	1.17 (1.04–1.32)	0.008

[a] The multivariate analyses included 831 cases with complete information for all covariates

cular diseases, or initial hyponatremia. The present data provide predictive factors for these pathogens that allow us to predict the patients particularly at risk and, therefore, to select individual initial empirical antimicrobial therapy more judiciously. However, therapeutic selection should be based on the severity of the infection, knowledge of epidemiology and resistance phenotypes in individual settings, and the required pharmacokinetic-pharmacodynamic parameters [14, 15].

Although our study did not prove a causal relationship between GNB pneumonia and 30-day mortality, data suggest that improvement in the management of patients with GNB pneumonia may reduce mortality. Further studies on the epidemiology and prognostic risk factors of severe CAP due to GNB are warranted to assess if early recognition of microbial etiology can modify the outcome of severe CAP. Given that comorbidity, underlying illness, and severity of pneumonia were significantly associated with GNB pneumonia, our data clearly support the management strategy according to clinical characteristics and severity of pneumonia that was recommended by ATS/IDSA [1].

This study has some limitations; it was an observational study that could not evaluate all possible risk factors for final clinical outcomes. In addition, this study was conducted mainly in large tertiary care medical centers with many patients who had serious underlying illnesses such as neoplastic diseases. Therefore, these data might not be applicable to the community hospitals.

In conclusion, GNB was not only a frequent etiology of severe CAP, but also an independent risk factor for mortality. Our data suggest that an initial empirical antimicrobial coverage of GNB including *P. aeruginosa* should be seriously considered in severe CAP cases, especially in patients with underlying malignancy, underlying cardiovascular diseases, smoking, septic shock, and hyponatremia.

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