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Address for Correspondence:
Sang-Bum Hong, MD
Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
E-mail: sbhong@amc.seoul.kr

Yong Pil Chong, MD
Department of Infectious Disease, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
E-mail: drchong@amc.seoul.kr

*Youjin Chang and Kyeongman Jeon contributed equally to this work.

ORCID iDs
Youjin Chang
https://orcid.org/0000-0002-4838-466X
Kyeongman Jeon
https://orcid.org/0000-0002-4822-1772
Sang-Min Lee
https://orcid.org/0000-0002-1388-9318
Young-Jae Cho
https://orcid.org/0000-0001-6943-4462

The Distribution of Multidrug-resistant Microorganisms and Treatment Status of Hospital-acquired Pneumonia/Ventilator-associated Pneumonia in Adult Intensive Care Units: a Prospective Cohort Observational Study

Youjin Chang [1*] Kyeongman Jeon [2*] Sang-Min Lee [3] Young-Jae Cho [4] Young Sam Kim [5] Yong Pil Chong [6] and Sang-Bum Hong [7]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, College of Medicine Inje University Sanggye Paik Hospital, Seoul, Korea
[2]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[3]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea
[4]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea
[5]Division of Pulmonology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[6]Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[7]Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

ABSTRACT

Background: It is essential to determine the distribution of the causative microorganisms in the region and the status of local antibiotic resistance for the proper treatment of hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP). This study aimed to investigate the occurrence and causative strains of HAP/VAP, distribution of resistant bacteria, use of antibiotics, and the ensuing outcomes of patients in Korea.

Methods: A multicenter prospective observational cohort study was conducted among patients with HAP/VAP admitted to the medical intensive care unit of 5 tertiary referral centers between August 2012 and June 2015. Patients' demographic and clinical data were collected.

Results: A total of 381 patients were diagnosed with HAP/VAP. Their median age was 69 (59–76) years and 71% were males. A majority of the patients (88%) had late-onset (> 5 days) HAP/VAP. One-quarter of the patients (n = 99) had at least one risk factor for multidrug-resistant (MDR) pathogens, such as prior intravenous antibiotic use within the last 90 days. Microbiological specimens were mostly obtained noninvasively (87%) using sputum or endotracheal aspirates. Pathogens were identified in 235 (62%) of the 381 patients. The most common bacterial pathogen was *Acinetobacter baumannii* (n = 89), followed by *Staphylococcus aureus* (n = 52), *Klebsiella pneumoniae* (n = 25) and *Pseudomonas aeruginosa* (n = 22). Most of isolated *A. baumannii* (97%)

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Young Sam Kim (iD)
https://orcid.org/0000-0001-9656-8482
Yong Pil Chong (iD)
https://orcid.org/0000-0003-1672-3185
Sang-Bum Hong (iD)
https://orcid.org/0000-0003-2737-7695

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Author Contributions
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and *S. aureus* (88%) were multidrug resistant. The most commonly used empirical antibiotic regimens were carbapenem-based antibiotics (38%), followed by extended-spectrum penicillin/β-lactamase inhibitor (34%). Glycopeptide or linezolid were also used in combination in 54% of patients. The 28-day mortality rate of the patients with HAP/VAP was 30% and the 60-day mortality was 46%. Patients who used empirical antibiotics appropriately had significantly lower mortality rates than those who did not (28-day mortality: 25% vs. 40%, $P = 0.032$; 60-day mortality: 41% vs. 55%, $P = 0.032$, respectively). Administration of appropriate empirical antibiotics (odds ratio [OR], 0.282; confidence interval [CI], 0.092–0.859; $P = 0.026$), Day 7 treatment failure (OR, 4.515; CI, 1.545–13.192; $P = 0.006$), and APACHE II score on day 1 (OR, 1.326; CI, 0.988–1.779; $P = 0.012$) were the factors that determined the 28-day mortality in patients with HAP who had identified bacteria as pathogens.

Conclusion: In HAP/VAP patients, there was a large burden of MDR pathogens, and their associated mortality rate was high. Proper selection of empirical antibiotics was significantly associated with the patient's prognosis; however, there was a discrepancy between major pathogens and empirical antibiotic therapy.

Keywords: Healthcare-associated Pneumonia; Ventilator-associated Pneumonia; Drug Resistance, Bacterial; Intensive Care Units; Treatment Outcome

INTRODUCTION

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are major nosocomial infections that increase mortality and morbidity in hospitals despite improvement in antibiotic treatment and supportive care, and dissemination of preventive measures.[1-4] The occurrence of HAP/VAP, especially if its pathogen is multidrug resistant, is associated with an increase in medical expenses,[5,6] and the suffering of patients and their families also increases. Moreover, poorly-treated HAP/VAP is a major cause of increased mortality.[1] Therefore, it is important to properly treat HAP/VAP. To do so, it is essential to determine the distribution of the causative microorganisms in the region and the status of local antibiotics resistance.[7,8] However, there are still insufficient data on this in Korea.[9,10]

The purpose of this study was to investigate the occurrence and causative strains of HAP/VAP, the distribution of resistant bacteria, the use of antibiotics, and the ensuing outcomes of patients in tertiary medical institutions in Korea.

METHODS

Study design
This was a multicenter prospective cohort study conducted with patients with HAP/VAP admitted to the intensive care units (ICUs) in five tertiary referral centers. The demographic and clinical data of the patients were collected.

Subjects
Patients were eligible if they were admitted to the ICU between August 2012 and June 2015 and if they met all of the following criteria: 1) Admission to the adult ICU, 2) Age > 18 years old, 3) New-onset HAP or VAP, and 4) If more than one HAP or VAP was present during hospitalization, only the first event was included.

The exclusion criteria were as follows: 1) Terminal illness with patient consent for 'Do Not Resuscitate (DNR)', 2) Terminal solid and hematologic malignancy without an active treatment plan, 3) A history of solid organ transplantation or bone marrow transplantation, 4) Pregnancy or less than 4 weeks postpartum, 5) Ongoing treatment for acquired immune deficiency syndrome, 6) Reception of antibiotics for more than 72 hours from another hospital, and 7) Transfer from other hospitals and subsequent development of new-onset pneumonia within 48 hours.

Data collection

Data on the following demographic and clinical parameters were prospectively collected: age, gender, body mass index (BMI), co-morbidities, reason for ICU admission, place of diagnosis for HAP/VAP, type of pneumonia, risk factors for multidrug-resistant (MDR) pathogens, time of diagnosis, severity scores as Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) score, clinical response as Clinical Pulmonary Infection Score (CPIS), pathogens, the presence of colonization for pathogens and antibiotic treatment. The following clinical outcome data were collected: day 3 improvement, day 7 failure, day 28 resolution, day 60 relapse, and 28-day and 60-day mortality.

Definitions

HAP was defined as pneumonia that occurred 48 hours or more after admission, which was not incubating at the time of admission.[1] VAP was defined as pneumonia that occurred more than 48–72 hours after endotracheal intubation.[1] Pneumonia was defined as new and persistent pulmonary infiltration plus at least two of following items: 1) A core body temperature $\geq 38.0°C$ or $\leq 36°C$, 2) leukocytosis with a white blood cell count of $\geq 11,000/mm^3$ or leukopenia with a white blood cell count of $\leq 4,000/mm^3$, and 3) purulent sputum or endotracheal aspirate. As clinical response indicators, Day 3 improvement was defined as day 3 CPIS reaching ≤ 6 or decreased by ≥ 2 points with respect to day 1 CPIS. Day 7 failure was defined as day 7 CPIS not being lower than 6 or failing to decrease ≥ 2 points with respect to day 1 CPIS, or if the PaO_2/FiO_2 ratio was not improving between day 1 and day 7. Day 28 resolution was defined as complete patient recovery and the stoppage of all antibiotics for pneumonia within 28 days. Day 60 relapse was defined pneumonia caused by the same pathogen occurring again within 4 weeks after antibiotics were stopped due to clinical improvement. The antibiotic therapy was judged as appropriate when the causative microorganism was susceptible to one or more of the prescribed antibiotics based on the in vitro antibiotic susceptibility testing. Bacteremia was defined as at least one positive blood culture for the causative organism of pneumonia. The isolated strain was recognized as the pathogen, only in the following cases; 1) quantitative culture of bronchoalveolar lavage samples ($\geq 10^4$ colony-forming unit [CFU]/mL), 2) quantitative culture of bronchoscopic aspirates ($\geq 10^5$ CFU/mL), 3) quantitative culture of endotracheal aspirates ($\geq 10^5$ CFU/mL), 4) semi-quantitative culture of endotracheal aspirates (moderate [or 3+] or higher), or 5) a strain cultured in adequate sputum (less than 10 epithelial cells in a low power field).

Statistical analysis

Continuous variables are reported as medians (interquartile range [IQR], 25–75%) or means ± standard deviation (SD), and categorical variables are reported as frequencies (percentages). To assess the differences between the groups, data were compared using the t-test or Mann-Whitney U test for continuous variables, while the χ^2 or Fisher's exact test was used to compare categorical variables. In the serial analysis of the severity score, each period was analyzed using paired t-test. For all analyses, a two-tailed P value < 0.05 was considered

statistically significant. To determine the prognostic factors for 28-day mortality, univariate analysis, and multivariate analysis were performed using logistic regression. Statistical analysis was performed using IBM SPSS version 24.0 (SPSS Inc., Chicago, IL, USA).

Ethics statement

This study was approved by the Asan Medical Center Institutional Review Board (study number 2012-0595). The need for informed consent was waived by the board.

RESULTS

Patient characteristics

A total of 381 patients were diagnosed with HAP/VAP during the period. Patient characteristics at the time of diagnosis are summarized at **Table 1**. The median age was 69 (59–76) years, and 71% of them were male. Solid malignant tumors (37%), chronic pulmonary disease (22%), and diabetes (22%) were the most frequently encountered co-morbidities. The reason for ICU admission was mainly acute respiratory failure (60%), followed by sepsis/ septic shock (15%). The most common place of diagnosis for HAP/VAP was the medical ICU (55%), followed by the general ward (32%). HAP and VAP were diagnosed in 54% and 46% of all patients, respectively. Of the 205 HAP patients, 121 (59%) were diagnosed in general ward, while the rest (41%) were diagnosed in the ICU. The mean APACHE II score on day 1 was 24 ± 7. One-quarter of HAP/VAP patients (n = 99) had prior intravenous antibiotic use within the last 90 days as a risk factor for MDR pathogens. Most of patients (88%) had late-onset (> 5 days) HAP/VAP. The median time from hospital admission to diagnosis for HAP/VAP was 11 (6–22) days. Then, the median time from mechanical ventilation to VAP was 9 (5–12) days.

Pathogens of HAP/VAP

Microbiological specimens were mostly obtained noninvasively (87%) using sputum or endotracheal aspirates. Out of the 381 patients, pathogens were identified in 235 (62%). Bacteria were the most common pathogens (94%), followed by viruses (4%). Among the 267 isolated pathogens, the most common bacterial pathogen was *Acinetobacter baumannii* (n = 89), followed by *Staphylococcus aureus* (n = 52), *Klebsiella pneumoniae* (n = 25), and *Pseudomonas aeruginosa* (n = 22) (**Table 2**). Most of the isolated strains of *A. baumannii* (97%) and *S. aureus* (88%) were multidrug resistant (**Fig. 1**). The bacteremia caused by the HAP/VAP pathogens was present in 29 (12%) patients. Twenty-six (12%) patients had poly-microbial infection. The results for each strain of bacteria and the distribution of major pathogens at each center are presented in **Supplementary Tables 1** and **2**.

MDR pathogens and colonization

Of the 223 patients whose pathogens were confirmed to be bacteria, 158 (71%) were infected by the MDR pathogens. Out of 250 isolated strains of bacteria, there were 171 (68%) MDR pathogens. The most common MDR pathogen was *A. baumannii* (50%), followed by *S. aureus* (30%) and *Stenotrophomonas maltophilia* (9%) (**Fig. 2**). In HAP, the most common MDR bacteria were methicillin-resistant *S. aureus* (40%) and carbapenem-resistant A. *baumannii* (33%), whereas in VAP, carbapenem-resistant *A. baumannii* (59%) accounted for the most, followed by methicillin-resistant *S. aureus* (26%) (**Table 3**). Of the patients whose pathogens were identified, 77 (35%) had colonization of the pathogen in the upper or lower respiratory tract from 2 weeks to 2 days before the onset of HAP/VAP (**Supplementary Table 3**).

Table 1. Baseline characteristics (n = 381)

Characteristics	Values
Age, yr	69 (59–76)
Sex, male	270 (71)
BMI, kg/m²	22 ± 4
Co-morbidities	
Malignancy	176 (46)
Solid tumor	141 (80)
Metastatic solid tumor	60 (16)
Hematologic	35 (20)
Chronic pulmonary disease	84 (22)
Diabetes mellitus	82 (22)
Cerebrovascular disease	46 (12)
Congestive heart failure/ischemic heart disease	38 (10)
Chronic kidney disease	38 (10)
Chronic liver disease	23 (6)
Moderate to severe liver disease	18 (5)
Modified CCI score	5.2 ± 2.8
Reason for ICU admission	
Acuter respiratory failure	230 (60)
Sepsis/septic shock	57 (15)
Postoperative care	18 (5)
Heart failure/acute coronary syndrome	16 (4)
Neurologic disease	15 (4)
Acute renal failure	8 (2)
Acute liver failure	5 (1)
Aspiration (macro)	5 (1)
Others	27 (7)
Location of diagnosis for HAP or VAP	
Medical ICU	211 (55)
General ward	123 (32)
Surgical ICU	21 (6)
Cardiovascular/cardiothoracic ICU	17 (5)
Neurologic/neurosurgical ICU	9 (2)
Type of pneumonia	
HAP	205 (54)
VAP	176 (46)
Risk factors for MDR pathogens	
HAP	n = 205
Prior intravenous antibiotic use within 90 days	61 (30)
VAP	n = 176
Prior intravenous antibiotic use within 90 days	38 (22)
Septic shock at time of VAP	48 (27)
Five or more days of hospitalization prior to the occurrence of VAP	152 (86)
Time of diagnosis	
Five or more days of hospitalization prior to the diagnosis of HAP/VAP	336 (88)
From hospital admission to diagnosis of HAP or VAP, days	11 (6–22)
From mechanical ventilation to VAP, days	9 (5–12)
Risk factors and preventive management for VAP	
Reintubation before diagnosis of pneumonia	36 (9)
Enteral feeding	135 (35)
Aspiration of subglottic secretion	149 (39)
Semi-recumbent position (> 30°)	209 (55)
APACHE II at day 1 of HAP or VAP	24 ± 7
Mechanical ventilation after diagnosis of HAP (n = 205)	166 (81)

Values are presented as number (%), mean ± standard deviation, or median (interquartile range).
BMI = body mass index, CCI = Charlson Comorbidity Index, ICU = intensive care unit, HAP = hospital-acquired pneumonia, VAP = ventilator-acquired pneumonia, MDR = multidrug-resistant, APACHE = Acute Physiology and Chronic Health Evaluation.

Table 2. The pathogens of HAP/VAP (n = 381)

Pathogens	Values
Patients with presence of pathogens	235 (62)
No. of pathogens, including polymicrobial infections	n = 267
Presence of bacteremia by pathogens	29 (12)
Patient No. with bacteria as pathogens	221 (94)
No. of bacteria including polymicrobial infection	n = 250
A. baumannii	89 (36)
S. aureus	59 (24)
K. pnemoniae	25 (10)
P. aeruginosa	22 (9)
S. maltophilia	16 (6)
E. faecium	6 (3)
E. coli	6 (2)
E. aerogenes	5 (2)
E. cloacae	3 (1)
S. pneumoniae	3 (1)
S. marcescens	2 (1)
C. freundii	2 (1)
A. xylosoxidans	2 (1)
Others	10 (4)
Patients with virus as pathogens	12 (5)
No. of virus	n = 12
Influenza A virus	5 (42)
RSV	2 (17)
PIV	1 (8)
Adenovirus	1 (8)
Influenza B virus	1 (8)
Human metapneumovirus	1 (8)
Rhinovirus	1 (8)
Patients with bacteria + virus as pathogens	2 (1)
Superinfection	n = 2
A. baumannii + RSV	1 (50)
S. pneumoniae + PIV	1 (50)

Values are presented as number (%).
HAP = hospital-acquired pneumonia, VAP = ventilator-associated pneumonia, RSV = respiratory syncytial virus, PIV = parainfluenza virus.
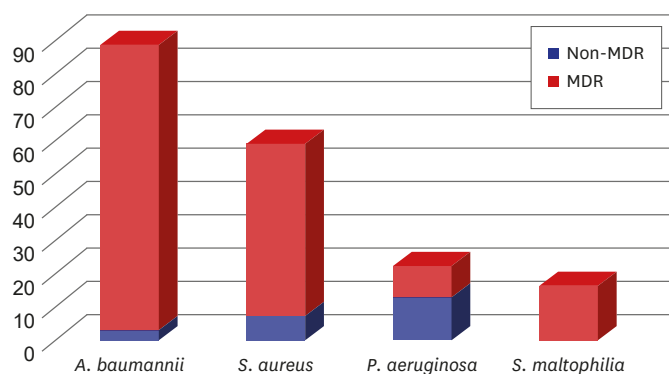
Fig. 1. Ratio of MDR bacteria in each major group of bacterial pathogens.
MDR = multidrug-resistant.

Previous antibiotics use

Within 4 weeks of onset of HAP/VAP, most patients (85%) received antibiotics for more than 48 hours, and the most common antibiotics were piperacillin/tazobactam (51%) and quinolone (56%) such as levofloxacin. In a significant number of patients, carbapenem (34%) and glycopeptide (40%) such as vancomycin were also used before the onset of HAP/VAP (**Supplementary Table 3**).
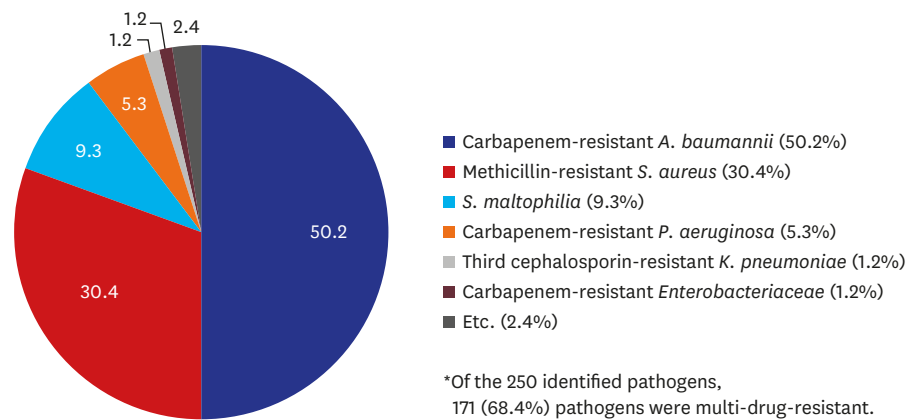
Fig. 2. Distributions of MDR bacteria.
MDR = multidrug-resistant.

- Carbapenem-resistant *A. baumannii* (50.2%)
- Methicillin-resistant *S. aureus* (30.4%)
- *S. maltophilia* (9.3%)
- Carbapenem-resistant *P. aeruginosa* (5.3%)
- Third cephalosporin-resistant *K. pneumoniae* (1.2%)
- Carbapenem-resistant *Enterobacteriaceae* (1.2%)
- Etc. (2.4%)

*Of the 250 identified pathogens,
171 (68.4%) pathogens were multi-drug-resistant.

Table 3. Distribution of MDR bacteria in HAP/VAP

Pathogens	Values
Patient No. with MDR bacteria as pathogens	n = 158
Total No. of MDR pathogens	n = 171
HAP	n = 205
Patient No. with MDR bacteria	n = 50
No. of identified MDR bacteria	n = 55
Methicillin-resistant *S. aureus*	22 (40)
Carbapenem-resistant *A. baumannii*	18 (33)
S. maltophilia	7 (13)
Carbapenem-resistant *P. aeruginosa*	5 (9)
Carbapenem-resistant *Enterobacteriaceae*	2 (4)
Others	1 (2)
VAP	n = 176
Patient No. with MDR bacteria	n = 108
No. of identified MDR bacteria	n = 116
Carbapenem-resistant *A. baumannii*	68 (59)
Methicillin-resistant *S. aureus*	30 (26)
S. maltophilia	10 (9)
Carbapenem-resistant *P. aeruginosa*	4 (3)
Others	3 (3)
Carbapenem-resistant *Enterobacteriaceae*	1 (1)

Values are presented as number (%).
MDR = multidrug-resistant, HAP = hospital-acquired pneumonia, VAP = ventilator-associated pneumonia.

Antibiotic treatment

Patients enrolled in the study received empirical antibiotics for the first 48 hours after the onset of HAP/VAP. The most commonly used antibiotic regimens were carbapenem-based antibiotics (38%), followed by extended-spectrum penicillin/β-lactamase inhibitors (34%). Intravenous colistin was initiated in 19 patients (5%). Quinolones were used together with other antibiotics in 40% of patients, and glycopeptides or linezolids were also used in combination in 54% of patients (**Table 4**).

Clinical responses according to scoring systems

As a clinical response, the SOFA score on day 1 was 8 (5–11), and then showed a significant decrease over days 3, 5, and 7 ($P < 0.001$). The CPIS was 6 (4–7) on day 1, and it also significantly decreased over days 3, 5, and 7 ($P < 0.001$).

Table 4. Empirical and subsequent antibiotic treatments (n = 381)

Variables	Values
Empirical antibiotics during the first 48 hours	
Carbapenem-based	144 (38)
Extended-spectrum penicillin/β-lactamase inhibitor	131 (34)
Glycopeptide or linezolid only	20 (5)
Intravenous colistin-based	19 (5)
Cefepime-based	15 (4)
Tigecycline-based	14 (4)
Quinolone only	12 (3)
Third cephalosporin-based	9 (2)
Carbapenem + tigecycline	8 (2)
Sulbactam-based	4 (1)
Intravenous colistin + tigecycline	4 (1)
Others	1 (0.3)
Combination therapy	
Quinolone	149/369 (40)
Glycopeptide or linezolid	196/361 (54)
Inhaled colistin	20 (5)
Subsequent antibiotics from the first 48 hour forth to 2 weeks	n = 377[a]
Carbapenem-based	137 (36)
Extended-spectrum penicillin/β-lactamase inhibitor	109 (29)
Intravenous colistin-based	30 (8)
Intravenous colistin + tigecycline	20 (5)
Cefepime-based	19 (5)
Quinolone only	15 (4)
Glycopeptide or linezolid only	15 (4)
Tigecycline-based	12 (3)
Third cephalosporin-based	11 (3)
Carbapenem + tigecycline	2 (1)
Sulbactam-based	2 (1)
Others	5 (1)
Combination therapy	
Quinolone	127 (34)
Glycopeptide or linezolid	176 (47)

Values are presented as number (%).
[a]Four patients with subsequent antibiotics from the first 48 hour forth to 2 weeks died.

Patient outcomes

Patient who showed improvement on day 3, that is, whose CPIS scores reached 6 points or less, or fell by 2 points or more with respect to the score on day 1, accounted for 33% of all patients. The rate of day 7 treatment failure, i.e., CPIS failing to fall below 6 or failing to decrease by at least 2 points with respect to the score on day 1, or the PaO_2/FiO_2 ratio failing to improve even after 1 week of treatment, was 41%. Within 28 days of starting treatment, 156 (41%) patients were able to completely stop antibiotics for pneumonia. Among the 156 patients who completed antibiotic treatment for pneumonia within 28 days, out of 25 patients whose pathogens were identified, there were 13 (52%) cases of pneumonia caused by the same pathogens within 4 weeks after stopping antibiotics (day 60 Relapse). The median length of MV was 17 (8–32) days. The 28-day mortality was 30%, and the 60-day mortality was 46%.

Outcomes according to the use of appropriate empirical antibiotics

The prognoses of patients differed significantly depending on whether or not they received appropriate empirical antibiotics. Of the 221 patients whose pathogens were identified as bacteria, 121 (55%) patients received appropriate empirical antibiotics. In the group that used appropriate empirical antibiotics, 42% of the patients were able to stop all antibiotics for pneumonia within day 28; however, when inappropriate used, only 21% of patients were

able to stop (*P* = 0.001). Also, patients who used empirical antibiotics appropriately had significantly lower mortality rates than those who did not (28-day mortality: 25% vs. 40%, *P* = 0.032; ICU mortality: 34% vs. 48%, *P* = 0.033; and 60-day mortality: 41% vs. 55%, *P* = 0.032, respectively). There were similar results in the comparison between the two groups according to whether the antibiotic used within 2 weeks after 48 hours was appropriate for the pathogen (**Supplementary Table 4**).

Prognostic factors of 28-day mortality

To determine the prognostic factors for 28-day mortality, multivariate analysis was performed with the six significant factors (*P* < 0.05) identified during univariate analysis (**Table 5**). As a result, five or more days of hospitalization prior to the occurrence of HAP/VAP (odds ratio [OR], 3.945; confidence interval [CI], 1.379–8.623; *P* = 0.008), APACHE II score on day 1 (OR,

Table 5. Univariate and multivariate analysis for 28-day mortality of all HAP/VAP patients

Variables (n = 381)	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, yr	1.009 (0.992–1.027)	0.315		
Male, sex	1.253 (0.779–2.015)	0.352		
Co-morbidities				
Metastatic solid tumor	1.711 (0.967–3.029)	0.065		
Chronic pulmonary disease	1.143 (0.679–1.926)	0.615		
DM with complications	0.935 (0.287–3.044)	0.911		
Cerebrovascular disease	0.708 (0.346–1.449)	0.344		
CHF/ischemic heart disease	0.821 (0.385–1.751)	0.609		
Chronic kidney disease	1.677 (0.744–3.781)	0.217		
Mod to severe liver disease	2.448 (0.945–6.338)	0.065		
Modified CCI score	1.082 (1.003–1.168)	0.042		
Reason for ICU admission				
Acute respiratory failure	1.247 (0.792–1.963)	0.339		
Sepsis/septic shock	0.995 (0.538–1.840)	0.986		
Postoperative care	0.454 (0.129–1.600)	0.219		
Heart failure/ACS	1.068 (0.362–3.146)	0.906		
Neurologic disease	0.349 (0.077–1.572)	0.170		
Acute renal failure	1.416 (0.333–6.028)	0.638		
Acute liver failure	3.581 (0.590–21.726)	0.165		
Aspiration (macro)	-	-		
Location of diagnosis				
Medical ICU	1.218 (0.781–1.898)	0.385		
General ward	0.955 (0.596–1.529)	0.848		
Surgical ICU	0.374 (0.108–1.295)	0.121		
Cardiac/Thoracic ICU	0.975 (0.335–2.834)	0.963		
Neuro/Neurosurgical ICU	0.851 (0.209–3.462)	0.821		
Risk factor for MDR organism				
Prior IV antibiotics use within 90 days	1.165 (0.711–1.908)	0.544		
Time of diagnosis				
Five or more days of hospitalization prior to the diagnosis of HAP/VAP	3.945 (1.637–9.506)	0.002	3.425 (1.379–8.623)	0.008
Risk factors and preventive management for VAP				
Enteral feeding	0.699 (0.436–1.119)	0.136		
Semi-recumbent position (> 30 degrees)	0.618 (0.398–0.961)	0.033	0.589 (0.363–0.957)	0.033
APACHE II at day 1	1.057 (1.024–1.092)	0.001	1.066 (1.029–1.105)	< 0.001
Identification of pathogens	1.286 (0.814–2.033)	0.281		
Presence of bacteremia	2.214 (1.041–4.708)	0.039		
Treatment response				
Day 3 improvement	0.553 (0.337–0.905)	0.018		
Day 7 failure	3.119 (1.981–4.911)	< 0.001	2.624 (1.635–4.212)	< 0.001

HAP = hospital-acquired pneumonia, VAP = ventilator-associated pneumonia, OR = odds ratio, CI = confidence interval, DM = diabetes mellitus, CHF = congestive heart failure, CCI = Charlson Comorbidity Index, ICU = intensive care unit, ACS = acute coronary syndrome, MDR = multidrug-resistant, APACHE II = Acute Physiology and Chronic Health Evaluation II.

1.066; CI, 1.029–1.105; $P < 0.001$), implementation of the semi-recumbent position (> 30 degrees) (OR, 0.589; CI, 0.363–0.957; $P = 0.033$), and day 7 failure (OR, 2.624; CI, 1.635–4.212; $P < 0.001$) were prognostic factors significantly associated with 28-day mortality.

Appropriate empirical antibiotics as a prognostic factor for 28-day mortality

When subgroup analysis was performed on patients whose pathogens were identified as bacteria, the administration of appropriate empirical antibiotics was a significant prognostic factor for 28-day mortality (OR, 0.282; CI, 0.092–0.859; $P = 0.026$) in HAP patients other than VAP along with day 7 failure (OR, 4.515; CI, 1.545–13.192; $P = 0.006$) and the APACHE II score on day 1 (OR, 1.108; CI, 1.023–1.200; $P = 0.012$) (**Table 6**).

Table 6. Univariate and multivariate analysis for 28-day survivor (n = 58) vs. non-survivor (n = 30) in HAP patients with identified bacterial pathogens

Variables (n = 88)	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, yr	0.995 (0.958–1.033)	0.781		
Male, sex	1.175 (0.475–2.906)	0.728		
Co-morbidities				
Metastatic solid tumor	4.109 (1.096–15.409)	0.036		
Chronic pulmonary disease	1.200 (0.390–3.694)	0.751		
DM with complications	-	-		
Cerebrovascular disease	0.694 (0.170–2.836)	0.611		
CHF/ischemic heart disease	0.251 (0.029–2.145)	0.207		
Chronic kidney disease	0.966 (0.084–11.099)	0.978		
Mod to severe liver disease	4.071 (0.354–46.838)	0.262		
Modified CCI score	1.297 (1.043–1.614)	0.020	1.326 (0.988–1.779)	0.060
Reason for ICU admission				
Acute respiratory failure	0.967 (0.369–2.537)	0.946		
Sepsis/septic shock	1.500 (0.313–7.186)	0.612		
Postoperative care	0.966 (0.084–11.099)	0.978		
Heart failure/ACS	-	-		
Neurologic disease	0.964 (0.166–5.592)	0.986		
Acute renal failure	-	-		
Acute liver failure	-	-		
Aspiration (macro)	-	-		
Location of diagnosis				
Medical ICU	1.396 (0.549–3.551)	0.483		
General ward	1.062 (0.437–2.583)	0.894		
Surgical ICU	-	-		
Cardiac/Thoracic ICU	1.996 (0.119–32.57)	0.637		
Neuro/Neurosurgical ICU	0.964 (0.166–5.592)	0.968		
Risk factor for MDR organism				
Prior IV antibiotics use within 90 days	1.229 (0.462–3.265)	0.680		
Time of diagnosis				
Five or more days of hospitalization prior to the diagnosis of HAP/VAP	2.106 (0.540–8.219)	0.284		
Risk factors and preventive management for VAP				
Enteral feeding	1.068 (0.352–3.240)	0.907		
Semi-recumbent position (> 30 degrees)	0.818 (0.324–2.065)	0.671		
APACHE II at day 1	1.114 (1.036–1.198)	0.004	1.108 (1.023–1.200)	0.012
Appropriate empirical antibiotics	0.415 (0.167–1.032)	0.059	0.282 (0.092–0.859)	0.026
Appropriate antibiotics from 48 hours to 2 weeks	0.499 (00.190–1.310)	0.158		
Presence of bacteremia	0.810 (0.194–3.385)	0.772		
Treatment response				
Day 3 improvement	0.459 (0.180–1.170)	0.103		
Day 7 failure	4.952 (1.921–12.765)	0.001	4.515 (1.545–13.192)	0.006

HAP = hospital-acquired pneumonia, OR = odds ratio, CI = confidence interval, DM = diabetes mellitus, CHF = congestive heart failure, CCI = Charlson Comorbidity Index, ICU = intensive care unit, ACS = acute coronary syndrome, MDR = multidrug-resistant organism, VAP = ventilator-associated pneumonia, APACHE II = Acute Physiology and Chronic Health Evaluation II.

DISCUSSION

This study aimed to identify the strain distribution and antibiotic selection of HAP/VAP patients in medical ICUs in Korea. The 28-day mortality rate of the patients with HAP/VAP was as high as 30%. The main pathogens responsible for HAP/VAP were *A. baumannii* and *S. aureus*, and most strains of *A. baumannii* and *S. aureus* were multidrug resistant. On the other hand, the empirical antibiotics, which were started within the first 48 hours of pneumonia, were mainly selected as carbapenem-based or extended-spectrum penicillin/β-lactamase inhibitor-based regimens, showing a discordance between the selection of antibiotics and the main strains. This suggests that a different standard is needed for empirical antibiotic selection in patients with HAP/VAP in domestic medical institutions.

The most commonly encountered strains in our study were *A. baumannii* and *S. aureus*. In HAP, *S. aureus* (22%), *A. baumannii* (19%), *K. pneumoniae* (15%), and *P. aeruginosa* (8%) were in that order, and in VAP, *A. baumannii* (46%), *S. aureus* (22%), *P. aeruginosa* (8%), and *S. maltophilia* (7%). In a prior study conducted in the 1990s, a multicenter surveillance of nosocomial infections was carried out in tertiary referral centers in Korea, *S. aureus* (45%) and *P. aeruginosa* (23%) were the two main strains identified in patients with nosocomial pneumonia.[11] Whereas, 10 years later, in a study conducted in Asian countries (including Korea), *A. baumannii* emerged as a major strain responsible for nosocomial pneumonia, especially VAP.[12] In terms of the distribution of MDR microorganisms, our study showed that the MDR rates of *A. baumannii*, *S. aureus,* and *P. aeruginosa* were 97%, 88%, and 41%, respectively. Compared to the data from the Asian countries whose rates were 82%, 82%, and 43%, respectively, the overall trends were in line with our results, although it was a little higher.[12] At the same time, the distribution of these strains in the European countries or the U.S was different.[4,13] In a previous study of 27 ICUs in nine countries in Europe,[13] the most common bacteria in nosocomial pneumonia patients who underwent mechanical ventilation were *S. aureus* (32%), *P. aeruginosa* (23%), and *A. baumannii* (19%). However, when comparing the three most common strains in each participating country, *A. baumannii* was not included in seven western European countries, which results were in line with U.S data.[4] On the other hand, in Greece and Turkey, the two remaining countries of the European study, the burden of *A. baumannii* was highest, in line with our results. *A. baumannii* is usually classified as a pathogen with low virulence.[2,14] The problem is that when antibiotic resistance is acquired, the range of alternative treatment options becomes limited. In the end, it is important to prevent *A. baumannii* from gaining drug resistance and to prevent further spread of strains that are already resistant to antibiotics.[15,16] In this regard, the role of infection control and antimicrobial stewardship in each country and each hospital is important. It could be the reason why the proportion of *A. baumannii* is lower in high-income countries than in middle and low-income countries. This suggests that the need for more thorough infection control should be further emphasized in Korea.

The present study demonstrated a significant difference in survival rate depending on whether the causative organisms were susceptible to the empirical antibiotics used within 48 hours of HAP/VAP. The results of this study are similar to those of previous ones.[17-20] In particular, in our study, the administration of adequate empirical antibiotics was a major determinant of the 28-day survival in HAP patients. The appropriate use of empirical antibiotics could help improve patients' prognosis; however, in reality, antibiotics are usually not administered properly as intravenous colistin was used as an empirical antibiotic in only about 5% of patients. If we look at the reasons, in the ICU setting, potentially-resistant

microorganisms were the main strains responsible for HAP/VAP in the present study. Considering the previously known local microbiological epidemiology,[12] it is appropriate to use empirical antibiotics targeting these multidrug resistant bacteria; however, the main reason for not doing so is the lack of investigation or understanding of local epidemiologic data, and, more importantly, the concerns about the unnecessary adverse effect and potential toxicity of antibiotics and the emergence of resistance.[21] In particular, for critically-ill patients who often suffer from renal insufficiency, physicians could hesitate to use potentially nephrotoxic antibiotics before the identification of the culprit microorganisms. Third, there is the issue of insurance. In Korea, insurance coverage for colistin is difficult if carbapenem-resistant microorganisms are not isolated. This will also be another reason why medical staff are hesitant to use it as an empirical antibiotic. Considering these aspects, this might be a difficult problem to solve, at least until drugs that can cover these bacteria without adversely affecting organs will be readily available.

Treatment response was evaluated on day 3, day 7, and day 28 in this study. Two-thirds of patients did not show a decrease in CPIS within 72 hours after the start of treatment, while 41% of patients had treatment failure after 1 week of treatment. Only 41% of all the patients completed treatment for pneumonia within 28 days; the remaining 59% either died or are still receiving antibiotics. We investigated whether the treatment response on day 3 and day 7 was associated with patients' 28-day mortality and found that day 3 improvement and day 7 failure were significantly associated with 28-day mortality in univariate analysis; however, in multivariate analysis, only day 7 treatment failure was significantly associated with 28-day mortality ($P < 0.001$). Of the 157 patients with treatment failure on day 7 (i.e., no decrease in CPIS or no improvement in the P/F ratio), pneumonia was not completely resolved in 124 (79%) on day 28; their 28-day mortality was 54%, while their 60-day mortality was 73%. Considering the previous literature that looked at the treatment response up to day 5 as an indicator of late treatment failure,[22] day 7 treatment failure was sufficient to evaluate the treatment response, and this study confirmed that it has a significant correlation with the patient's prognosis. Thus, when the patients do not improve within 7 days, taking into account the possibility of continuing deterioration, more careful attention should be paid to whether antibiotics are appropriately selected, whether sufficient supportive care is provided, and to prevent additional VAP. This study revealed that the implementation of the semi-recumbent position (> 30 degrees) was an important factor associated with a lower 28-day mortality. The semi-recumbent position has already been identified as a method of preventing VAP in several studies.[23-25] Our results suggested that the sufficient application of this method reduces the risk of additional pneumonia in mechanically-ventilated HAP/VAP patients, which led to better outcomes.

Although this was a prospective multicenter study, it had some limitations. First, the five medical centers that participated in the study consisted of only tertiary hospitals, which is not representative of all patients with HAP/VAP in Korea. Second, in patients who started empirical therapy with broad-spectrum antibiotics, there is a possibility that the adverse effects of the antibiotics used might have affected the patients; however, this has not been specifically investigated. Third, since we only recruited HAP/VAP patients who were admitted to the ICU, not all HAPs that occurred in the hospitals were recruited, as HAPs that occurred and improved in the general ward were not investigated.

In this study, the strains of bacteria responsible for HAP/VAP in tertiary referral hospitals in Korea were associated with a huge burden of MDR bacteria. Proper selection of empirical

antibiotics was significantly associated with an improvement the patient's prognosis. In contrast, it was demonstrated that there was a discrepancy between initial empirical antibiotic selection and major strains. In selecting antibiotics, the adverse effects of drugs should be considered important. Future studies based on these domestic microbiologic data are needed to establish criteria for selecting appropriate antibiotics considering all of these factors. In addition, a prompt judgment of the treatment response and prevention of additional pneumonia should not be neglected.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
The distribution of poly-microbial infection

Click here to view

Supplementary Table 2
Distribution of major pathogens of HAP/VAP at each center

Click here to view

Supplementary Table 3
Colonization and previous antibiotics use before the occurrence of HAP/VAP

Click here to view

Supplementary Table 4
Outcomes according to appropriate antibiotics used from after 48 hours to 2 weeks

Click here to view

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