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Original article

Healthcare associated pneumonia: An old concept at a hospital with high prevalence of antimicrobial resistance

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Abstract: ***Background:*** One of several reasons that the concept of healthcare-associated pneumonia (HCAP) was dismissed was the same presence of multidrug resistant organism (MDRO) between community-acquired pneumonia and HCAP at countries with the low prevalence of antimicrobial resistance (AMR). However, this finding could be unsuitable for countries with the high rates of AMR. ***Methods:*** A prospective observational study was conducted at the respiratory department of Cho Ray hospital from September 2015 to April 2016. All adult patients suitable for community acquired pneumonia (CAP) with risk factor for healthcare-associated infection were included. ***Results:*** We found out 130 subjects. The median age was 71 years (interquartile range 57-81). The male/female ratio was 1.55:1. Prior hospitalization was the most common risk factor for healthcare-associated infection. There were 35 cases (26.9%) with culture-positive (sputum and/or bronchial lavage). Isolated bacteria included *Pseudomonas aeruginosa* (9 cases), *Klebsiella pneumoniae* (9 cases), *Escherichia coli* (4 cases), *Acinetobacter baumannii* (6 cases), and *Staphylococcus aureus* (7 cases) with the characteristic of AMR similar to the bacterial spectrum associated with hospital-acquired pneumonia. ***Conclusion:*** MDROs were detected frequently in CAP patients with risk factor for healthcare-associated infection at the hospital with the high prevalence of AMR. This requires the urgent need to evaluate risk factors for MDRO infection in community-onset pneumonia when the concept of HCAP is no longer used.

Keywords: Antibiotic; antimicrobial resistance; healthcare-associated pneumonia.

1. INTRODUCTION

Pneumonia is one of leading etiologies associated bacterial infection causing death in which the bacterial characteristic of antimicrobial resistance (AMR) contributes mainly this outcome. The concept of healthcare-associated pneumonia (HCAP) was proposed as a separate clinical entity because the HCAP patient showed the high risk of pneumonia induced by multidrug resistant organism (MDRO) [1, 2]. However in the late 2016, Infectious Disease Society of America (IDSA)/ American Thoracic Society (ATS) removed this clinical entity [3] because these reasons as follows:

- Several published studies in countries with low prevalence of AMR revealed the presence of AMR organisms similar between community-acquired pneumonia (CAP) and HCAP.
- Poor outcomes did not depend on pneumonia with MDRO but mainly related to age and comorbidities.
- Underlying characteristics of HCAP patients were also associated with the risk for MDRO infection.

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We hypothesized that the prevalence of AMR would influence microbial characteristics of HCAP. Vietnam has the emergence of resistant bacteria because (1) antibiotics are described widely in community and (2) they could be sold easily without requirement of prescription at private pharmacies [4]. Moreover, central Vietnamese hospitals are often crowded to facilitate nosocomial infection. Our study aimed to identify microbial characteristics of CAP patients with risk factor for healthcare-associated infection at the Vietnamese hospital with high prevalence of AMR.

2. MATERIALS AND METHOD

A prospective observational study was conducted at the respiratory department of Cho Ray hospital from September 2015 to April 2016. Cho Ray hospital was noticed as one of Vietnamese hospitals with the high rate of AMR through the VINARES project 2012-2013 [4]. All adult patients suitable for diagnosis of HCAP were included. Diagnostic criteria of HCAP were applied according to IDSA/ATS guideline 2005 [2]. In detail, a defined diagnosis of HCAP was established when patients obtained two following requirements:

- Having pneumonia (CAP or pneumonia developing during 48 hours after admission): new or progressing infiltration on chest x-ray combined with at least one primary criterion (cough up sputum, fever > 38^0 Celsius) or at least two secondary criteria (pleuritic pain, shortness of breath, confusion, crackles or consolidation syndrome, white blood cells > 12000/mm^3).
- Having one of risk factors for healthcare-associated infection such as: hospitalizing ≥ 2 days during 90 days before this episode of pneumonia, residence in nursing home or long-term healthcare facility, taking intravenous medication or chemotherapy during 30 days before this episode of pneumonia, periodic hemodialysis or peritoneal dialysis.

Table 1. Characteristics of 130 healthcare-associated pneumonia subjects

Features		Value
Age (year, IQR)		71 (57-81)
Male (%)		60.8
Duration of symptom (days, IQR)		4 (3-7)
Symptoms	Fever (%)	80.8
	Cough up sputum (%)	84.6
	Dry cough (%)	15.4
	Chest pain (%)	56.9
Past medical history	Smoking (%)	61.5
	Chronic obstructive pulmonary disease (%)	21.5
	Pulmonary tuberculosis (%)	34.6
	Diabetes mellitus (%)	23.8
	Kidney failure (%)	13.8
	Malignancy (%)	3.8
	Taking systemic corticosteroid (%)	69.2
	Prior antibiotic use (%)	46.9
Respiratory failure (%)		88.5
Shock (%)		7.7
White blood cell (G/L, IQR)		12.7 (9.3-18.1)
CRP (mg/l, IQR)		79.3 (44.0-113.9)
Procalcitonin (ng/l, IQR)		1.4 (0.5-8.9)
Duration of hospital stay (days, IQR)		13 (10-15)
Complications	Lung abscess (%)	4.6
	Pleural effusion-empyema (%)	20.0
	Pneumothorax (%)	1.5
Outcomes	Death (%)	10.0
	Survival (%)	90.0

CRP: C-reactive protein; IQR: Interquartile range

Exclusion criteria in our study included early hospital readmission (≤ 7 days), rapid test positive for human immunodeficiency virus, sputum smear positive for acid fast bacilli or other evidences for diagnosis of pulmonary tuberculosis, non-bacterial pneumonia, or no diagnosis of pneumonia at discharged time.

Samples of spontaneous sputum with good quality (> 25 white blood cells and < 10 squamous cells per low-power field) and/or bronchial lavage were cultured to detect pathogens. Isolated bacteria were classified multidrug-resistant (MDR) pathogen if it was non-susceptibility to ≥ 1 agent in ≥ 3 antimicrobial categories, extensively drug-resistant (XDR) pathogen if it was non-susceptibility to at least 1 agent in all but 2 or fewer antimicrobial categories, or pandrug-resistant (PDR) pathogen if it was non-susceptibility to all agents in all antimicrobial categories [5].

All subjects gave their informed consents for inclusion. This study protocol was approved by the Ethics Committee of University of Medicine and Pharmacy at Ho Chi Minh City.

Our subjects were divided into two groups with culture-positive and culture-negative. Chi-Square test and Mann-Whitney U test were used to find out difference between two groups, respectively categorical variables and continuous variables. All statistical tests were performed using SPSS software, version 16.0 (SPSS, Inc., Chicago, IL, USA). Value $p < 0.05$ was considered as significantly statistical difference.

3. RESULTS

A total of 130 CAP patients with risk factor for healthcare-associated infection were included in this study, 62.3% of whom was age ≥ 65. Risk factors for healthcare-associated infection included 87.7% cases with hospitalization ≥ 2 days during recent 90 days, 9.2% cases with receiving intravenous medication, and 3.1% with periodic hemodialysis. Demographic and clinical characteristics of study population were presented in Table 1. Duration of medical history < 7 days appeared in 87.7% cases.

Table 2. Types of isolated bacteria

Isolated bacteria	Number (%)
Pseudomonas aeruginosa	9 (25.7%)
Klebsiella pneumoniae	9 (25.7%)
Escherichia coli	4 (14.5%)
Acinetobacter baumannii	6 (17.1%)
Staphylococcus aureus	7 (20.0%)
A total of culture-positive	35 (26.9%)

Table 3. Antimicrobial resistant characteristics of isolated bacteria

Type of pathogen (total number)	Classification of AMR	Rate of AMR	Comparable to study of hospital-acquired pneumonia
Pseudomonas aeruginosa (9)	MDR	4/9	Similar to *P. aeruginosa* in the study of Dao Ngoc Duy et al, Douglas J. Biedenbach et al [6, 7]
	XDR	2/9	
	PDR	0/9	
Klebsiella pneumoniae (9)	MDR	4/9	Similar to *K. peumoniae* in the study of Le Tien Dung [8] and the study of Tran Minh Giang et al [9]
	XDR	1/9	
	PDR	0/9	
	ESBL (+)	6/9	
Acinetobacter baumannii (6)	MDR	5/6	Similar to *A. baumannii* in the study of Duong Minh Ngoc et al [10] and the study of Tran Van Ngoc et al, Douglas J. Biedenbach et al [7, 11]
	XDR	1/6	
	PDR	0/6	
Escherichia coli (4)	MDR	3/4	Similar to *E. coli* in the study of Le Tien Dung [8]
	XDR	1/4	
	PDR	0/4	
	ESBL (+)	3/4	
Staphylococcus aureus (7)	MDR	7/7	N/A
	XDR	0/7	
	PDR	0/7	
	MRSA (+)	7/7	

AMR: antimicrobial resistance; ESBL: Extended-spectrum beta-lactamase; MDR: Multidrug-resistant; MRSA: Methicillin-resistant Staphylococcus aureus; PDR: Pandrug resistant; XDR: Extensively drug-resistant

Bacteria were isolated in 26.9% cases (80% gram-negative bacteria and 20% gram-positive bacteria), 82.9% of whom were from sputum culture and 17.1% of whom were from bronchial lavage culture. Types of isolated bacteria were similar to the spectrum of bacteria inducing hospital-acquired pneumonia (HAP) which reported in previous studies at Vietnamese hospitals (Table 2). The antimicrobial susceptibility tests of isolated bacteria are shown in Table 3.

Our study showed similar characteristics between groups with culture-positive and culture-negative (Table 4). However the prevalence of male sex, past history of pulmonary tuberculosis, and the blood level of procalcitonin were higher in the culture-positive group and the patients with culture-positive had more long-term of hospitalization, except for the lower rate of renal failure.

4. DISCUSSION

Our study showed that CAP with risk factor for healthcare-associated infection often developed among elderly patients with comorbidities who needed medical attention frequently, an important feature observed in previous studies [12-14]. Risk factors for healthcare-associated infection could vary between different geographic areas. Prior hospitalization was the most common risk factor in our study, whilst residence in nursing home was not reported as other studies at Korea [12, 13, 15]. The majority of subjects (78.5%) were transferred to from local hospitals, a feature similar to the study of Jong Hoo Lee et al 2012 [13]. Duration of hospital stay in our study was the same as the study of Hye Kyeong Park et al 2010 [12]. The rate of deaths (10%) was also consistent with other studies (rates of death range from 5% to 33%) [16].

The rate of bacterial isolation in this study (26.9%) seemed lower than other studies, such as: Hye Kyeong Park et al (35.7%) [12], June H. Ahn et al (38.3%) [15], Jong Hoo Lee et al (57.3%) [13], and Andrew J. Labelle et al (49.5%) [17]. HCAP studies conducted before 2005 described mainly *Staphylococcus aureus* and *Pseudomonas aeruginosa* as MDRO [1] but our study showed more diversity of MDROs (*Klebsiella pneumonia, Escheria Coli, Acinetobacter baumannii*) similar to studies at Korea [12, 14, 15]. Moreover our study revealed no *Streptococcus pneumonia* isolated and types of isolated bacteria analogous to that associated with HAP

[8]. This result was in contrast to the study by Eva Polverino et al 2013 [18] conducted in Spain, a country with low rate of AMR. This difference could be associated with distinct characteristics of the respiratory department of Cho Ray hospital, a central tertiary hospital with severe patients (frequent hospitalization), admitting patients who were treated antibiotics at grassroots hospitals without improvement, overloaded status, and the high rate of AMR [19]. This also implies that the concept of HCAP at our hospital could be separated clearly with CAP but undifferentiated with HAP. Besides the rates of MDR and XDR bacteria among 35 cases of isolated bacteria were 65.7% and 14.3%, respectively. This feature of AMR supported more evidence about concordance of the spectrum of bacteria inducing HCAP and HAP in our study. Although the concept of HCAP is now dismissed, we recommended that risk factors of healthcare-associated infection, especially prior hospitalization, should be considered as risk for community-onset pneumonia with MDRO at our hospital [20, 21].

Table 4. Comparison between healthcare-associated pneumonia groups with culture-positive and culture-negative

Characteristics		**Culture-positive (n = 35)**	**Culture-negative (n = 95)**	***p*-value ($p < 0.05$)**
Age (years, IQR)		70 (61-79)	72 (57-82)	0.700
Male		80.0%	53.7%	**0.006**
Duration of symptom (days, IQR)		3 (2-7)	4 (3-7)	0.414
Symptoms	Cough	100%	100%	1.000
	Fever	85.7%	79.0%	0.385
	Chest pain	65.7%	53.7%	0.219
Respiratory failure		85.7%	89.5%	0.552
Past medical history	Diabetes mellitus	22.9%	24.2%	0.872
	COPD	22.9%	21.1%	0.824
	Pulmonary tuberculosis	54.3%	27.4%	**0.004**
	Renal failure	2.9%	17.9%	**0.028**
	Taking corticosteroid	62.9%	71.6%	0.339
	Prior antibiotic use	48.6%	46.3%	0.819
White blood cells (G/l, IQR)		12.0 (9.2-17.5)	12.7 (9.3-19.8)	0.618
CRP (mg/L, IQR)		78.5 (52.8-145.7)	80.0 (40.0-112.6)	0.458
Procalcitonin (ng/L, IQR)		2.1 (0.8-12.7)	1.3 (0.5-5.4)	**0.032**
Complications		37.1%	22.1%	0.084
Death		14.3%	9.2%	0.323
Duration of hospital stay (days, IQR)		14 (12-16)	12 (10-15)	**0.020**

COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; IQR: Interquartile range

Our study revealed several different features between pneumonia groups with culture-positive and culture-negative. First, the higher rate of male in culture-positive group could reflect the effective capacity of expectoration versus the habit of less expectoration in female which was influenced by sociocultural factors. Second, post-tuberculosis patients could develop structural sequelae at lung to facilitate bacterial colonization which would contribute the higher rate of positive cultures. Third, pneumonia group with culture-positive had the higher level of procalcitonin and more the long-term of hospitalization that were consistent with the study of Andrew J. Labelle et al [17]. We also analyzed the initial empirical antibiotic therapy both two groups which showed no difference in the initial antibiotic strategy (carbapenem + levofloxacin/ciprofloxacin or betalactam/betalactamase inhibitor + levofloxacin/ciprofloxacin were common strategies). Therefore the long-term of hospitalization in culture-positive group could be associated with the change of antibiotics according to antibiotic susceptibility testing and consequently required at least seven days to complete the new antibiotic strategy. Although the rate of death in culture-negative group was lower than that in culture-positive group but no statistical significance. Together with the low level of procalcitonin, we questioned that "whether there was any difference in the pathogen between two groups or not?". More detailed, pneumonia in culture-negative group could be induced by virus, atypical bacteria, or pathogens unable to be isolated because of taking antibiotics previously at grassroots hospitals.

Our study had several limitations. We did not evaluate atypical bacteria which were mentioned in previous HCAP studies [15, 18]. We need to collect more information relating to the initial antibiotic therapy at grassroots hospitals to analyze pathogen in culture-negative group comprehensively. The low rate of cases with isolated bacteria could influence the final conclusion because this result of culture might not have presented the real spectrum of bacteria inducing CAP with risk factor for healthcare-associated infection. We recommend using more sensitive method to detect pathogen such as real-time polymerase chain reaction in further research to strength the result of study.

Conclusion

In conclusion, our study showed that MDROs were detected frequently in CAP patients with risk factor for healthcare-associated infection at a hospital with the high prevalence of AMR. Prior hospitalization should be considered as risk factor for MDRO pneumonia at our hospital. Although the concept of HCAP is no longer used, further studies are necessary to evaluate the factors (which were related to the previous classification of HCAP) for risk of MDRO infection among community-onset pneumonia.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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