Prevalence of Causative Bacteria, Therapeutic Choices of Antimicrobacterials and Clinical Outcomes among Patients with Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia in A General Hospital

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Original Article

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาความชุกของเชื้อแบคทีเรียที่เป็นสาเหตุ ความไวต่อยาต้านจุลชีพ ยาต้านจุลชีพที่เป็นทางเลือกรักษา และผลลัพธ์ทางคลินิก รวมถึงปัจจัยที่สัมพันธ์กับความล้มเหลวทางการรักษาในผู้ป่วยโรคปอดอักเสบในโรงพยาบาล (HAP) และปอดอักเสบที่เกี่ยวข้องกับเครื่องช่วยหายใจ (VAP) **วิธีการศึกษา:** การศึกษาย้อนหลังครั้งนี้รวบรวมผู้ป่วยโรคปอดอักเสบที่รักษาตัวในโรงพยาบาลหัวหิน ซึ่งเป็นโรงพยาบาลทั่วไป ระหว่างเดือนมกราคม - ธันวาคม พ.ศ. 2556 เกณฑ์คัดเลือกผู้ป่วย คือ อายุมากกว่า 18 ปีขึ้นไป และผู้ป่วยโรคปอดอักเสบที่ตรงตามนิยามของ HAP และ VAP ทั้งนี้ ระบุเชื้อที่เป็นสาเหตุจากเชื้อที่เพาะได้จากผู้ป่วยปอดอักเสบ ผลลัพธ์ทางคลินิกได้แก่ อัตราความล้มเหลวทางการรักษาและอัตราตายภายใน 30 วัน **ผลการศึกษา**: มีผู้ป่วยร่วมการศึกษา 106 ราย เป็นเพศชายร้อยละ 56.6% มีค่ามัธยฐานของอายุเท่ากับ 72 ปี (พิสัย 18 - 95 ปี) ผู้ป่วยร้อยละ 81.1 มีโรคร่วม และร้อยละ 27.4 เป็นผู้ป่วยในหออภิบาล (ไอซียู) ในผู้ป่วย 91 รายที่เพาะแล้วพบเชื้อ พบเชื้อแบคทีเรียจำนวน 155 สายพันธุ์ในสิ่งส่งตรวจเสมหะ โดยเป็นผู้ป่วย HAP 46 *ราย และ* VAP 60 *ราย โดยใน* HAP เชื้อแบคทีเรีย 3 ลำดับแรก คือ *A. baumannii* (ร้อยละ 23.8), *P. aeruginosa* (*ร้อยละ* 20.6) และ *K. pneumoniae* (ร้อยละ 17.5) *และใน* VAP *พบ* เชื้อแบคทีเรีย 3 ลำดับแรก คือ *A. baumannii* (ร้อยละ 32.6), *P. aeruginosa* (ร้อยละ 18.5) และ *S. aureus* (*ร้อยละ* 22.8) พบว่ายา imipenem และ meropenem เป็นทางเลือกรักษาที่ดีสำหรับเชื้อ *K. pneumoniae* ในขณะที่ยา vancomycin เป็นยาที่ครอบคลุมเชื้อ methicillin-resistant *S. aureus* ที่ดี จากผู้ป่วย 106 ราย พบอัตราตายและความล้มเหลวทางการรักษาร้อยละ 17.9 และ 34 ตามลำดับ โดยการใช้ยาต้านจุลชีพอย่างเหมาะสมและการติดเชื้อ multi-drug resistant *A. baumannii* เป็นปัจจัยที่สัมพันธ์กับความล้มเหลวทางการรักษา (ค่า odds ratios เท่ากับ 0.126 และ 3.624, ตามลำดับ) **สรุป:** การศึกษาครั้งนี้มีความชุกของเชื้อแบคทีเรียที่เป็นสาเหตุคล้ายคลึงกับโรงพยาบาลขนาดใหญ่ ส่วนการใช้ยาต้านจุลชีพอย่างเหมาะสมและการติดเชื้อ MDR-*A. baumannii* สัมพันธ์กับผลลัพธ์ทางการรักษาที่ไม่พึงประสงค์

คำสำคัญ: เชื้อจุลชีพที่เป็นสาเหตุ, ผลลัพธ์ทางคลินิก, โรคปอดอักเสบ

Abstract

Objectives: To assess the prevalence of etiologic bacteria of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), the antibiotic susceptibility of the isolated pathogens and the prescribed antimicrobial therapy. Relationship between select factors and clinical outcomes was tested. **Methods:** This retrospective study included HAP or VAP patients admitted to Hua-hin Hospital, a general hospital, from January to December 2013. Patients aged 18 or older and diagnosed with HAP or VAP were included. The bacteria isolated from HAP or VAP patients were listed as etiologic pathogens and the clinical outcomes were classified as treatment failure and 30-day mortality rate. Results: Of the 106 patients recruited, their median age was 72 years (range: 18 - 95 years). It was found that 56.6% of 106 patients were male, 81.1% had comorbid diseases and 27.4% were admitted to the intensive care unit. With 15 patients with negative sputum culture, 91 patients contributed 155 isolated organisms. Of the 46 HAP cases, *A. baumannii* (23.8%), *P. aeruginosa* (20.6%) and *K. pneumoniae* (17.5%) were the most frequently found isolated organisms; while *A. baumannii* (32.6%), *P. aeruginosa* (18.5%) and *S. aureus* (22.8%) were the most frequently identified among 60 VAP cases. Imipenem and meropenem were a good option for *K. pneumoniae*; while vancomycin remained the best drug against methicillin-resistant *S. aureus*. Of the 106 cases, the crude 30-day mortality rate and treatment failure were 17.9% and 34%, respectively. The appropriate antimicrobial treatment and multi-drug resistant *A. baumannii* were the two factors significantly associated with treatment failure in the opposite directions, with odds ratios of 0.126 and 3.624, respectively. **Conclusion**: Our findings illustrated the pattern of causative pathogens in a general hospital that seemed to have the same trouble as in a larger-sized hospital. The appropriate antimicrobial treatment and multi-drug resistant *A. baumannii* were related to the unfavorable outcome.

Keywords: causative pathogens, clinical outcome, pneumonia

Introduction

Pneumonia, especially nosocomial infection (NI), is a major public health problem and a leading cause of hospital mortality in Thailand. Danchaivijitr et al. performed a cross-sectional study among 42 hospitals nationwide in March 2001. They found that lower respiratory tract was the first-ranked source of infection (34.1%).[1] A subsequent study by the same author in 2006 found that lower respiratory tract infection remained the nosocomial infection with the highest prevalent.[2]

Moreover, patients with pneumonia during a hospital stay, either hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP), had poorer clinical outcomes. Limpawattana et al. performed a health situation analysis of hospitalized Thai older persons in 2010 and found that mortality rates were highest in the elders with pneumonia.[3] According to the frequent unfavorable outcomes, there has been an increasing need to optimize antibiotic utilization to treat most common causative pathogens. Many previous studies indicated that the inappropriate treatment, either a use of antibiotics with no pathogen coverage or a delay to start antibiotics within 24 hours of sepsis, caused a higher mortality rate and a longer period of hospitalization.[4-6] In this drug resistance era, it has been highly difficult to optimize the antimicrobial selection for causative pathogens, particularly those multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, extended spectrum beta-lactamases (ESBL)-producing *Klebsiella pneumoniae* and methicillin-resistant *Staphylococcus aureus*. This frustrating situation was supported by the work of Luna et al. which showed that the coverage rates of empirical therapy in patients with VAP caused by *Acinetobacter species*, *Klebsiella pneumoniae*, *P. aeruginosa* and *S. aureus* were only 15.6%, 23.5%, 46.2% and 21.9%, respectively.[7]

The proportions of various etiologic microorganisms differed among levels of hospitals. However, the studies on pathogenic microorganism prevalence have been done mostly in tertiary health care settings especially medical school hospitals. The types of pathogens and their antimicrobial susceptibility in community and general hospitals could however have been different from the ones of medical schools. It was found that *A. baumannii* was the most common isolated pathogen in the three university hospitals[8-10], whereas *Klebsiella* spp. was the most frequently isolated organism from nosocomial pneumonia patients in a general hospital on the Eastern Thailand.[11]

In Hua-hin Hospital, a general hospital in Prachuap Khiri Khan province, the problem of antimicrobial resistance has been increasing. Recently, the study in our institution by Santimaleeworagun and colleagues found that the appropriate antimicrobial therapy defined as receiving at least one antimicrobial agent within 24 hours was associated with a significant lower 30-day mortality rate.[12] Other factors specific to this general hospital, however, have not been known.

Therefore, the objective of this present study was to determine the prevalence of causative pathogens of HAP and VAP and the antimicrobial susceptibility of the most common isolated organisms. Select factors were also tested for the association with the clinical outcomes in HAP and VAP patients.

Materials and Methods

This retrospective review study gathered the patients' data from an electronic medical records database. We included the patients with HAP or VAP between January and December 2013, admitted to Hua-hin Hospital, a 400-bed general hospital in Prachuap Khiri Khan province, Thailand. The protocol was approved by the research ethics committee of our institute with a waiver for informed consent [No. 18/2557; issued on December 19th, 2014].

Definitions

Pneumonia, based on the American Thoracic Society criteria, was diagnosed by a set of clinical features. These criteria included 1) having at least 2 of 4 signs of the systemic inflammatory syndrome (SIRS) (body temperature of > 38 ºC or < 36 ºC, respiratory rate of > 20 beats per minute, heart rate of > 90 beats per minute, leukocytosis defined as white blood cells (WBC) of > 12,000 cells per millilitre, or leukopenia defined as WBC of < 4,000 cells per millilitre), and 2) clinical symptoms consisting of cough, purulent sputum or pleuritic chest pain. In addition, patients had to be confirmed by lung imaging, usually with a new or persistent infiltrate seen on chest radiography.

Hospital-acquired pneumonia (HAP) was defined as a pneumonia in the patient admitted to the hospital for more than 48 hours. *Ventilator-associated pneumonia* (VAP), a subset of HAP, was defined as patients diagnosed with pneumonia after being on a mechanical ventilator for more than 48 hours.[13] *Multi-drug resistant* (MDR) pathogen was defined as an isolated microorganism resistant to greater than 3 classes of antimicrobials. *The appropriate antimicrobial therapy* in this study was defined as receiving antimicrobials that could cover the causative pathogen within 24 hours after the diagnosis of the suspected pneumonia. *Septic shock* was referred to the non-responsiveness to the fluid loading in patients with hypotension (i.e., mean arterial blood pressure of < 65 mmHg) and one or more vasopressor was indicated

to normalize blood circulation. Shocks of other origins, i.e., hypovolemic, cardiogenic shock, and obstructive, were ruled out. *Impaired renal function* was defined as a serum creatinine elevation of more than 50% of the baseline level. *Steroid use* was defined as a use of a prednisolone dose of > 10 mg daily for more than 2 weeks.

In terms of clinical outcomes, *treatment failure* included a failure and death. Patients with failure were those whose clinical symptoms got worse or their antimicrobial agent against causative pathogens had to be changed or added. Death was the patient who died within 30 days of HAP or VAP acquisition.

Participants

The inclusion criteria in this study consisted of 1) age of 18 years or older 2) being diagnosed with pneumonia, and 3) being compatible with the definition of HAP or VAP. Those patients transferred to the other hospital and whose follow-up information could not be obtained were excluded from the study. Patients with incomplete medical record data were also excluded.

Data collection

The medical records and the report of antimicrobial susceptibility were retrieved from the computer database for clinical information. Such information consisted of age, sex, underlying diseases, ward type, mechanical ventilator use, septic shock status, hepatic function, renal function, immunocompromised status, antimicrobial regimen (dosage and duration), antimicrobial susceptibility, length of hospital stay, source of infection, vital sign and clinical outcomes.

The identification of pathogens from the good quality sputum (i.e., WBC of > 25 cells and epithelial cell of < 10 cells) was verified by morphology, Gram stain, standard biochemistry tests, coagulase test, and selective media for culturing, if available. Susceptibility testing was based on the antimicrobial susceptibility testing (AST) performed routinely with the disk diffusion method, also called Kirby-Bauer method. This method provided qualitative results reported as susceptible (S), intermediate (I) or resistant (R), based on the interpretation of clinical and laboratory standards.[14]

Statistical analysis

The descriptive statistics were used to depict characteristics of the participants, antibiotic regimens, antimicrobial susceptibility results and clinical outcomes (i.e., mortality rate and treatment failure), among patients with HAP or VAP. Chi-square or Fisher's exact test, as appropriate, was used to determine the correlation between the categorical factors and clinical outcomes. For continuous data, Student t-test or Mann-Witney U test, as appropriate, was used to compare the mean or median, respectively, between the two-group clinical outcomes. All significant variables in the univariate analysis at a *P*-value of < 0.1 were further tested by the logistic regression analysis. The dependent variable was treatment failure, whereas the outcome-related independent variables previously described included age[15,16], underlying disease[15], type of pathogen[17,18], multiple-bacterial infection[17], steroid use[16], renal function impairment[16], septic shock[9,15], bacteremia[19] and the appropriate antimicrobial treatment.[19] Data analysis was conducted by using PSPP version 0.8.5, an open-source statistical software, available at https://www.gnu.org/software/pspp/. Statistical significance level for all tests was set at a type I error of 5%.

Results

During the study period, 106 participants with HAP (n = 46) or VAP (n = 60) were recruited. Of these 106 patients, slightly more than half were male (56.6%). Their median age was 72 years with a range of 18 - 95 years. Eighty-six patients (81.1%) had co-morbid diseases and 29 patients (27.4%) were admitted to the intensive care unit. The median time prior to HAP or VAP acquisition was 8 days with a range of 2 - 157 days (Table 1).

Causative pathogens and their antimicrobial susceptibility

According to the negative sputum culture in 15 cases (14.2%), the isolated organisms in 91 patients with HAP or VAP were obtained (Table 2). Of these 91 cases, mono- and poly-microbial isolations were found in 35 cases (38.5%) and 56 cases (61.5%), respectively, resulting in 155 isolated organisms. Among these 155 isolates, the majority were Gram negative bacteria (81.3%). The top-three pathogens included *A. baumannii*, *P. aeruginosa* and *S. aureus*. For HAP cases, the most frequently found isolated pathogens were *A. baumannii* followed by *P. aeruginosa* and *K. Pneumonia*; while *A. baumannii*, *P. aeruginosa* and *S. aureus* were the top-three isolated organisms among VAP cases.

Table 1 Characteristics of patients with hospital-acquired pneumonia or ventilator-associated pneumonia (N = 106).

Characteristics	N (%)
Gender: male	60 (56.9)
Age, years, median (range)	72 (18 - 95)
Being treated in the intensive care unit	29 (27.4)
Duration before HAP or VAP diagnosis (days), median (range)	8 (2 - 157)
Length of hospitalization after HAP or VAP diagnosis (days), median (range)	12 (1 - 57)
Underlying diseases*	86 (81.1)
Hypertension	41 (30.5)
Diabetes mellitus	21 (15.7)
Cerebrovascular disease	16 (11.9)
Dyslipidemia	15 (11.2)
Heart failure	14 (10.5)
Anemia	14 (10.5)
Chronic obstructive pulmonary disease	13 (9.7)
Mechanical ventilator use	54 (51.9)

* For a given patient, more than one disease could be found.

Table 2 The causative pathogens (N = 155 isolates) in patients with hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP).

	Number of isolates (%)	
	HAP (n = 63 isolates)	VAP (n = 92 isolates)
A. baumannii	15 (23.8)	30 (32.6)
Multi-drug resistant strains	15	27
P. aeruginosa	13 (20.6)	17 (18.5)
Multi-drug resistant strains	1	2
K. pneumonia	11 (17.5)	14 (15.2)
Third generation cephalosporin non-susceptible strains	4	0
S. aureus	7 (11.1)	21 (22.8)
Methicillin resistant S. Aureus		19
E. coli	8 (12.7)	2 (2.2)
Enterobacter spp.	4 (6.4)	6 (6.5)
Proteus spp.	1 (1.6)	2 (2.2)
Streptococcus spp.	1 (1.6)	0
Other Gram negative bacilli	3 (4.7)	0
Total	63 (100)	92 (100)

Table 3 shows the antimicrobial susceptibility of the most common isolated organisms. Colistin was still the most active agent against *P. aeruginosa* whereas the carbapenems such as imipenem and meropenem were an effective choice for *K. pneumoniae*. Vancomycin remained an effective antibiotic to cover *S. aureus* while fosfomycin was no longer an option.

Table 3 The antimicrobial susceptibility of *A.baumannii, P. aeruginosa*, *K. pneumoniae* and *S. aureus.*

Antimicrobials	Number of isolates (%)			
	A. baumannii (n = 45)	*P. aeruginosa* (n = 30)	*K. pneumoniae* (n = 25)	*S. aureus* (n = 28)
Amikacin	4 (6.7)	27 (90)	22 (88)	-
Gentamicin	3 (6.7)	27 (90)	18 (72)	4 (14.3)
Ceftazidime	2 (4.4)	24 (80)	12 (48)	-
Ceftriaxone	-	-	13 (52)	-
Ciprofloxacin	2 (4.4)	27 (90)	-	-
Cefoperazone/ Sulbactam	2 (4.4)	20 (67)	-	-
Imipenem	2 (4.4)	22 (73.3)	25 (100)	-
Meropenem	2 (4.4)	22 (73.3)	25 (100)	-
Ertapenem	-	-	24 (100)	-
Colistin	-	30 (100)	-	-
Cefoxitin	-	-	-	4 (14.3)
Clinadamycin	-	-	-	4 (14.3)
Fosfomycin	-	-	-	4 (14.3)
Vancomycin				28 (100)

Clinical outcomes

Regarding the clinical outcomes among 106 pneumonia cases, rates of crude 30-day mortality and treatment failure were 17.9% and 34%, respectively. According to the type of pneumonia, patients with HAP (n = 46) vs. VAP (n = 60) had comparable crude 30-day mortality rates of 13.0% and 15.0%, respectively. However, treatment failure rate of those with HAP (23.9%) was slightly higher than that among VAP patients (16.7%). Of all the 91 patients with positive bacterial culture, only 65 patients (71.4%) received appropriate antimicrobial treatment covering the causative pathogens.

Predictive factors of clinical outcomes

All variables as factors potentially related to the treatment failure were analyzed in the univariate analysis. These variables included age, underlying disease, type of pathogens, multiple-bacterial infection, steroid use, renal function impairment, septic shock, bacteremia and the appropriate antimicrobial treatment. The results from univariate analyses showed that the only two factors significantly associated with treatment failure were MDR-*A. baumannii* infection and the appropriate antimicrobial treatment. In the following logistic regression analysis, the appropriate antimicrobial treatment and MDR-*A. baumannii* infection remained the factors significantly related to the treatment failure with the adjusted ORs of 0.126 (95% CI: 0.043 - 0.365) and 3.624 (95% CI: 1.269 - 10.345), respectively.

Discussions and Conclusion

Among 106 cases of pneumonia, we found more VAP (60) than HAP (46) cases. Of these 106 cases, sputum cultures were successfully obtained in 91 patients resulting in 155 isolated organisms. The first two most found organisms were *A. baumannii* and *P. aeruginosa* both in VAP and HAP cases; while *K. pneumoniae* and *S. aureus* were the third most identified organisms for VAP and HAP cases, respectively. Imipenem and meropenem were the good choice for *K. pneumoniae*; while vancomycin remained a good drug to cover MRSA. Among all 106 pneumonia cases, the crude 30-day mortality rate was 17.9% while the treatment failure rate was 34.0%. While the appropriate antimicrobial treatment was a significant protective factor of the treatment failure, multi-drug resistant *A. baumannii* was a significant aggravating one.

Etiologic pathogens for HAP and VAP are Gram negative bacilli, specifically *P. aeruginosa* and *A. baumannii* and Gram positive cocci, especially *K. pneumoniae* and *S. aureus.* As expected, we also found causative bacteria similar to those in several reports in Thailand. Reechaipichitkul et al. studied the causative agents among HAP and VAP patients at a tertiary care teaching hospital in the north-east of Thailand from 2008 to 2009. They found that nearly 70% of HAP cases were caused by *P. aeruginosa, A. baumannii*, and *K. pneumoniae*; and about 70% of VAP were caused by *A. baumannii, P. aeruginosa,* and *K. pneumoniae*.[10] These pathogens were also found in a study by Weerarak et al. in a medical school hospital in the central part of Thailand. They found that *A. baumannii* was the most common organism followed by *K. pneumoniae, P. aeruginosa* and *MRSA*.[9] Another study by Luksamijarulkul and co-workers on the etiology of nosocomial pneumonia at a provincial hospital revealed that *Klebsiella* spp. was the number-one cause.[11] At present, previous studies and our present study revealed that bacterial pathogens of nosocomial pneumonia were common among different levels of healthcare settings. However, a considerable discrepancy in the prevalence of individual pathogenic bacteria among various levels of healthcare institutes was of concern. For any given institutes, this discrepancy emphasizes the importance of the tailor-made antimicrobial selection approach. Continuous local studies on the microbial sensitivity should be encouraged.

The appropriate regimen for empirical therapy was evaluated from the antimicrobial agents covering the most causative bacteria. However, there were no susceptibility results of colistin against *K. pneumoniae* and *A. baumannii* because of the absent breakpoint for disk diffusion based on clinical laboratory standard in 2014. Fortunately, the colistin-resistant Gram negative bacteria were scant in Thailand.[10,20]; hence, colistin remained the therapeutic choice for Enterobacteriaceae and *A. baumannii.*

As a medium-sized general hospital, mortality rate in our study (17.9%) was much lower than that in a medical teaching hospital (45.9%) as reported by Weerarak and colleagues.[9] This discrepancy could be attributable to the fact that a large proportion of patients in Weerarak et al. study were severely ill (42.5%) which led them to a rapid mortality. Another possible reason was that a larger proportion of patients in our study (71.4%) received appropriate antimicrobial therapy while only 58.9% in the work of Weerarak and colleagues did.

In this study, we found the appropriate therapy a significant protective factor for the treatment failure. This predictor was also reported in a few previous studies.[21-23] Importantly, another factor such as HAP or VAP caused by *A. baumannii* was significantly correlated with a poor clinical outcome. Tseng and colleagues suggested that the patients with *A. baumannii* VAP had a higher mortality than with other organisms.[18]

There were certain limitations in our study conduct and hence cautions with our findings. With various sensitivity of resistant bacteria, appropriate antimicrobials in each hospital were different. In our study, APACHE II score, predictor associated with mortality patient with pneumonia[19], was not calculated; hence, biased results could be expected. However, the patient characteristic information such as age, renal function, and shock, which were important parameters in APACHE II score, had been already included in the univariate analysis.

This study has illustrated the pattern of causative pathogens for VAP and HAP in a general hospital comparable to that in a larger-sized hospital. Additionally, the appropriate antimicrobial treatment was associated with a better treatment outcome. In the resistant organism era, the individualized antibiotic regimen is a strategy to improve the quality of pneumonia treatment.

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