CAUSATIVE AGENTS AND RESISTANCE AMONG HOSPITAL-ACQUIRED AND VENTILATOR-ASSOCIATED PNEUMONIA PATIENTS AT SRINAGARIND HOSPITAL, NORTHEASTERN THAILAND

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Abstract. Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) have an impact on health care costs and mortality. The aim of this study was to identify the causative agents, antibiotics prescribed, cost of treatment and drug resistance trends among HAP and VAP patients at a tertiary-care hospital in northeastern Thailand during 2008 and 2009. The incidences of HAP in 2008 and 2009 were 0.7/1,000 and 0.55/1,000 hospital days, respectively. The incidences of VAP in 2008 and 2009 were 13.6/1,000 and 12.6/1,000 ventilator days, respectively. About 70% of HAP were caused by *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*; and 70% of VAP were caused by *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae*. The ranking in the causative agents of HAP and VAP was not different, but more antimicrobial resistant organisms were seen in 2009. More than half of the costs of nosocomial infection treatment in 2008 and 2009 were the costs for HAP and VAP, 16.8 and 17.5 million Baht, respectively. Fewer *A. baumannii* and *P. aeruginosa* isolates were sensitive to carbapenems. Only one-fifth of *A. baumannii* isolates were sensitive to cefoperazone/sulbactam. The only two antimicrobial agents with consistently good activity against *A. baumannii* were tigecycline (~ 85%) and colistin (~ 99%). Fifty-seven point six percent of *P. aeruginosa* isolates were sensitive to ceftazidime, 72.4% were sensitive to piperacillin/tazobactam, 95.9% were sensitive to netilmycin and 99.2% were sensitive to colistin. Forty-seven percent of *K. pneumoniae* isolates were extended spectrum beta-lactamase sensitive to carbapenems. Methicillin-resistant *S. aureus* was the cause of 6 - 7% of HAP/VAP cases in our study.

Keywords: hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), causative agents, cost, drug resistance, Thailand

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INTRODUCTION

The most common nosocomial infection is nosocomial pneumonia (NP), which included hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) (ATS and IDSA, 2005).

HAP is defined as a pulmonary infection that occurs after 48 hours of hospitalization; it affects an average of 5 - 10 cases per 1,000 hospital admissions (Celis *et al*, 1988). Hospital stays in patients with HAP are increased by 7 - 9 days (ATS and IDSA, 2005). A pulmonary infection that develops after a patient has been on ventilator for more than 48 hours is defined as VAP; it occurs in 9 - 27% of all intubated patients (Chastre and Fagon, 2002). VAP occurs in an average of 10 - 41.7 per 1,000 ventilator days (Chastre and Fagon, 2002). Mechanically ventilated patients are 6 - 21 times more likely to develop NP than non-ventilated patients, because the endotracheal tube bypasses upper respiratory tract defenses, allowing pooling of oropharyngeal secretions and prevents effective cough (Torres *et al*, 1990). The intensive care unit (ICU) length of stay in patients with VAP is increased by an average of 6.1 days, and increases the cost of hospitalization by an average of USD 40,000 per patient (Safdar *et al*, 2009). The mortality rates for HAP vary between 14% and 20% and for VAP between 33% and 50% (ATS and IDSA, 2005; Torres *et al*, 2009).

The selection of antimicrobial agents in cases of NP is an important determinant of hospital mortality. Appropriate antimicrobial therapy, when initiated early, reduces mortality among critically-ill patients with NP (Torres *et al*, 2010). Common pathogens causing NP include aerobic gram-negative bacilli, such as *P. aeruginsa*, *E. coli*, *K. pneumoniae*, and *Acinetobacter* spp. Gram-positive cocci, such as *Staphylococcus aureus*, and particularly methicillin-resistant *S. aureus* (MRSA), have emerged rapidly worldwide as a cause of NP (ATS and IDSA, 2005; Torres *et al*, 2009, 2010). The frequencies of antibiotic resistant gram-negative bacteria, including multi-drug resistant (MDR) pathogens, causing NP vary from hospital to hospital, by patient population, exposure to antibiotics and the type of ICU patient (Torres *et al*, 2010). Usually pathogens causing VAP are more resistant to antimicrobials than those causing HAP (Chawla, 2008). Local surveillance of the pathogens causing NP and their resistance patterns is important to guide initial empiric antimicrobial therapy.

The objective of this study was to determine the incidences and etiologies of HAP and VAP, antimicrobial use, treatment costs and resistance patterns over two consecutive years at Srinagarind Hospital, a tertiary care center in northeastern Thailand.

MATERIALS AND METHODS

We conducted a cross sectional, hospital-based, active surveillance study of NP among adults hospitalized at Srinagarind Hospital, an 800-bed tertiary care hospital, between January 2008 and December 2009. The criteria used to diagnose HAP were: 1) a pulmonary infection developing 48 hours after hospital admission, 2) a chest radiograph showing a new pulmonary infiltration, and 3) at least two of the three following features: a temperature >38.3°C or <36.5°C, leukocytosis (WBC >12,000 cells/mm^3) or leukopenia (WBC <4,000 cells/mm^3) and purulent tracheal secretions (ATS and IDSA, 2005; Torres *et al*, 1994). The criteria for diagnosing VAP were: 1) a pulmonary infection developing 48 hours after the onset of mechanical ventilation, 2) a chest radiograph showing a new pulmonary infiltration, and 3) at least two of the three following features: a temperature >38.3°C or <36.5°C, leukocytosis (WBC >12,000 cells/mm^3) or leukopenia (WBC <4,000 cells/mm^3) and purulent tracheal secretions (ATS and IDSA, 2005;

Table 1
Agents causing HAP at Srinagarind Hospital in 2008 and 2009.

HAP in 2008 (n = 176) 0.7/1,000 hospital days		HAP in 2009 (n = 136) 0.55/1,000 hospital days	
1. *P. aeruginosa*	27.9%	1. *P. aeruginosa*	29.7%
2. *A. baumannii*	22.8%	2. *A. baumannii*	22.6%
3. *K. pneumoniae*	20.8%	3. *K. pneumoniae*	19.4%
4. *E. coli*	7.6%	4. MRSA	9.0%
5. *Enterobacter* spp	7.1%	5. *E. coli*	4.5%
6. MRSA	6.1%	6. *Enterobacter* spp	4.5%
7. *Xanthomonas maltophila*	4.1%	7. *Xanthomonas maltophila*	4.5%
8. MSSA	2.0%	8. *Proteus mirabilis*	1.9%
9. *Serratia* spp	1.6%	9. *Serratia* spp	1.9%
10. Other	0%	10. Other	2%

MRSA, methicillin resistant *Staphylococcus aureus*; MSSA, methicillin sensitive *S. aureus*

Torres *et al*, 1994). Exclusion criteria were: 1) patients with pneumonia on or prior to admission or mechanical ventilation, 2) a pulmonary infiltrate from other causes, such as heart failure, atelectasis, adult respiratory distress syndrome (ARDS), an acute pulmonary embolism, an alveolar hemorrhage, or pulmonary tuberculosis.

The incidences of and pathogens causing HAP and VAP were reported by infection control ward nurses (ICWNs) from each ward following the above criteria and were confirmed by the infection control nurses (ICNs) of the hospital. The type and duration of antibiotic prescribed by the physician to treat the HAP or VAP were identified and recorded. More than one type of antibiotic may have been used in each case. The cost of antibiotic therapy was also calculated and compared with the cost of other nosocomial infections in the hospital. The drug susceptibility pattern for each pathogen was recorded.

Ethical approval

The Ethics Committee of the Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand, approved this study.

Statistical analysis

Descriptive statistics were used for the study data. The means and standard deviations were calculated for continuous data; and numbers and percentages were calculated for categorical data.

RESULTS

One hundred seventy-six patients developed HAP in 2008 (0.7/1,000 hospital days) and 136 patients developed HAP in 2009 (0.55/1,000 hospital days). The three most common pathogens causing HAP for both years were: *P. aeruginosa*, *A. baumannii* and *K. pneumoniae*, accounting for 70% of the total cases of HAP (Table 1). *P. aeruginosa* caused nearly 30% of HAP pathogens, *A. baumannii* and *K. pneumoniae* caused an average 20% for each. Methicillin resistant *Staphylococcus aureus* (MRSA) was the sixth most common cause of HAP (6.1%) in 2008 and the fourth most common cause of HAP (9.0%) in 2009.

The three most commonly used an-

Table 2
Antibiotics used to treat HAP at Srinagarind Hospital in 2008 and 2009.

Ranking of antibiotic use for HAP in 2008 (n = 215)		Ranking of antibiotic use for HAP in 2009 (n = 186)	
1. Piperacillin/tazobactam	23.7%	1. Piperacillin/tazobactam	17.2%
2. Imipenem	14.9%	2. Ceftazidime	16.1%
3. Ceftazidime	13.5%	3. Imipenem	14.0%
4. Cefoperazone/sulbactam	7.9%	4. Colistin	10.8%
5. Vancomycin	5.6%	5. Vancomycin	8.6%
6. Ceftriazone	5.1%	6. Amoxycillin/clavulanate	7.5%
7. Levofloxacin	4.7%	7. Cefoperazone/sulbactam	5.4%
8. Amoxycillin/clavulanate	4.2%	8. Meropenem	4.8%
9. Amikacin	2.8%	9. Clindamycin	3.8%
10. Meropenem	2.3%	10. Levofloxacin	1.6%
11. Colistin	1.4%	11. Cloxacillin	1.1%
12. Tigecycline	0.9%	12. Amikacin	0.5%
13. Cloxacillin	0.9%	13. Tigecycline	0%
14. Other	12.1%	14. Other	8.6%

tibiotics for HAP in 2008 and 2009 were piperacillin/tazobactam, ceftazidime and imipenem (Table 2). Colistin was used in the treatment of 1.4% of cases for HAP in 2008 and 10.8% of cases in 2009.

VAP was the most common nosocomial infection at our hospital during the study period. The goal of our hospital is to keep the number of episodes of VAP to fewer than 12/1,000 ventilator days. Two hundred eighty-six and 276 patients had VAP in 2008 and 2009, respectively. There were 13.6/1,000 ventilator days of VAP in 2008 and 12.6/1,000 ventilator days of VAP in 2009. The three most common pathogens causing VAP were the same for 2008 and 2009: *A. baumannii*, *P. aeruginosa* and *K. pneumoniae*, comprising 70% of the total cases of VAP (Table 3). *A. baumannii* caused nearly 30 - 40% of VAP pathogens, *P. aeruginosa* ~25% and *K.pneumoniae* ~15%. The percent cases caused by MRSA remained unchanged between 2008 and 2009 (6 - 7%).

The five most commonly used antibiotics to treat VAP in 2008 were: cefoperazone/sulbactam (14%), imipenem (13.7%), piperacillin/tazobactam (11.5%), cetazidime (11%) and colistin. (9.1%). The five most commonly used antibiotics to treat VAP in 2009 were: colistin (17.3%), imipenem (14.5%), piperacillin/tazobactam (12.1%), cefoperazone/sulbactam (11.2%) and meropenem (7.1%) (Table 4).

The total cost of treating all nosocomial infections at our hospital was around thirty million Baht per year for 2008 and 2009 (Table 5). VAP was the most expensive nosocomial infection to treat for 2008 and 2009 due to resistant organisms requiring treatment with expensive antibiotics.

The drug susceptibility patterns for HAP and VAP cases during the study were shown in Tables 6, 7 and 8. Eighty-three

Table 3
Agents causing VAP at Srinagarind Hospital in 2008 and 2009.

VAP in 2008 (n = 286) 13.6/1,000 ventilator days		VAP in 2009 (n = 276) 12.6/1,000 ventilator days	
1. *A. baumannii*	26.9%	1. *A. baumannii*	38.9%
2. *P. aeruginosa*	25%	2. *P. aeruginosa*	22%
3. *K. pneumoniae*	15.4%	3. *K. pneumoniae*	12.3%
4. *Enterobacter* spp	8.8%	4. *Xanthomonas maltophila*	7.5%
5. MRSA	7.2%	5. *Enterobacter* spp	6.3%
6. *Xanthomonas maltophila*	7.2%	6. MRSA	6.0%
7. *E. coli*	4.8%	7. *E. coli*	2.9%
8. *Serratia* spp	2.4%	8. *Serratia* spp	1.9%
9. MSSA	0.8%	9. *Proteus mirabilis*	1%
10. Other	1.5%	10. Other	1.2%

MRSA, methicillin resistant *Staphylococcus aureus*; MSSA, methicillin sensitive *S. aureus*

Table 4
Antibiotics used to treat VAP at Srinagarind Hospital in 2008 and 2009.

Ranking of antibiotic use for VAP in 2008 (n = 373)		Rank of antibiotic use for VAP in 2009 (n = 421)	
1. Cefoperazone/sulbactam	14%	1. Colistin	17.3%
2. Imipenem	13.7%	2. Imipenem	14.5%
3. Piperacillin/tazobactam	11.5%	3. Piperacillin/tazobactam	12.1%
4. Ceftazidime	11%	4. Cefoperazone/sulbactam	11.2%
5. Colistin	9.1%	5. Meropenem	7.1%
6. Vancomycin	7.3%	6. Vancomycin	6.2%
7. Meropenem	5.4%	7. Ceftazidime	4.3%
8. Amikacin	4.8%	8. Amikacin	3.1%
9. Levofloxacin	4.3%	9. Cloxacillin	3.1%
10. Cloxacillin	3.5%	10. Cotrimoxazole	3.1%
11. Tigecycline	2.7%	11. Tigecycline	2.1%
12. Amoxycillin/clavulanate	2.1%	12. Levofloxacin	2.1%
13. Clindamycin	2.1%	13. Ceftazidime	1.9%
14. Other	8.5%	14. Other	11.9%

point three percent of *P. aeruginosa* isolates were sensitive to piperacillin/tazobactam in 2008 and 72.4% were sensitive in 2009. Seventy-four point three percent of *P. aeruginosa* isolates were sensitive to ceftazidime in 2008 and 57.6% were sensitive in 2009. Twenty-four point two percent *P. aeruginosa* isolates were sensitive to ciprofloxacin in 2008 and 10% were sensitive in 2009. Twenty-eight percent of *P. aeruginosa* isolates were sensitive to meropenem in 2008 and 16.9% in 2009. Ninety-five

Table 5
Cost of antibiotics treating nosocomial infections at Srinagarind Hospital in 2008 and 2009.

Type of nosocomial infection	Cost in 2008 (Baht)	Cost in 2009 (Baht)
VAP	10,495,672	12,209,424
HAP	6,405,616	5,308,639
UTI, catheter related	4,031,067	3,622,903
UTI, non-catheter related	2,265,326	1,722,539
BSI, central line related	1,842,708	1,974,502
BSI, non-central line related	2,561,825	2,160,893
SSI, clean	245,938	251,230
SSI, clean contaminate	1,847,210	1,575,738
SSI, contaminate	1,127,839	151,984
SSI, dirty	42,672	0
Miscellaneous	3,064,161	2,822,473
Total	33,930,034	31,800,325

VAP, ventilator associated pneumonia; HAP, hospital acquired pneumonia; UTI, urinary tract infection; BSI, blood stream infection; SSI, skin and soft tissue infections; miscellaneous, other nosocomial infections (*eg,* cellulitis, bed sore infections, newborn eye infections, bronchitis, sinusitis).

percent of *P. aeruginosa* isolates were sensitive to netilmycin and 98% were sensitive to colistin in both years.

Twenty-four point six percent of *A. baumannii* isolates were sensitive to cefoperazone/sulbactam in 2008 and 17% were sensitive in 2009. About 40% of *A. baumannii* isolates were sensitive to netilmycin and amikacin. Nearly 100% of *A. baumannii* isolates were sensitive to colistin and 85% were sensitive to tigecycline.

Forty-seven percent of *K. pneumoniae* isolates were extended spectrum beta lactamase (ESBL) producers. Non-ESBL producing *K. pneumoniae* isolates were sensitive to third generation cephalosporins and all ESBL-producing *K. pneumoniae* isolates were resistant to third generation cephalosporins. Fifty-three point three percent of ESBL-producing *K. pneumoniae* isolates were sensitive to cefoperazole/sulbactam in 2008 and 47% were sensitive in 2009. Ninety-nine percent of ESBL-producing *K. pneumoniae* isolates were sensitive to the carbapenems tested.

MRSA was the most common gram-positive bacteria causing HAP and VAP. Fifty-one percent of *S.aureus* isolates were resistant to oxacillin. One hundred percent of *S.aureus* isolates were sensitive to vancomycin. Ninety-two point eight percent of *S.aureus* isolates were sensitive to fosfomycin in 2008 and 89% were sensitive in 2009. Ninety-four point nine percent of *S.aureus* isolates were sensitive to fusidic acid in 2008 and 89.8% were sensitive in 2009.

DISCUSSION

At our hospital, a tertiary care center in northeastern Thailand, VAP and HAP were the first and second most common nosocomial infections. The incidences of

Table 6
Drug sensitivities among *P. aeruginosa* and *A. baumannii* isolates from sputum cultures in 2008 and 2009.

Antimicrobial	*P. aeruginosa*				*A. baumannii*			
	2008		2009		2008		2009	
	n	% S	*n*	% S	*n*	% S	*n*	% S
Amikacin	1,214	85.4	1,241	71.2	933	38.8	1,205	40
Gentamicin	1,203	84	1,236	78.4	924	33.1	1,203	41.9
Netilmicin	1,184	94.2	1,234	95.9	874	37.6	1,164	42.3
Cefotaxime	-	-	-	-	924	2.8	1,193	3.4
Ceftazidime	1,198	74.3	1,237	57.6	922	32.3	1,199	28.9
Cefpirome	181	5	398	1.8	605	0.8	824	1.3
Cefoperazone/subactam	184	17.4	401	9	568	24.6	827	17
Ampicillin/sulbactam	174	0.6	396	0.3	593	17.2	822	9.7
Piperacillin	1,126	72.4	1,153	56	-	-	-	-
Piperacillin/tazobactam	1,178	83.3	1,230	72.4	888	31.9	1,173	28.3
Levofloxacin	1,186	73.4	1,198	59.5	888	36.7	1,158	31.3
Ciprofloxacin	186	24.2	400	10	605	0.8	827	2.9
Imipenem	192	22.9	407	25.6	604	3	826	5.1
Meropenem	182	28	402	16.9	605	3.1	823	5.5
Cotrimoxazole	-	-	-	-	928	30.8	1,188	28.4
Tigecycline	63	3.2	57	5.3	594	94.3	788	85.2
Colistin	155	98.1	399	99.2	511	99.4	725	99.4

n = number of isolates tested for sensitivity.
% S = percent of isolates sensitive to tested antimicrobial.

VAP in 2008 and 2009 were high (13.6 and 12.6 per 1,000 ventilator days), compared to other Asian countries (Chawla, 2008). The incidence of VAP in Korea has been reported to be between 3.5 and 7.1 per 1,000 ventilator days (Kim *et al*, 2000). In India, the incidence of VAP was reported to be 8.9 per 1,000 ventilator days (Chawla, 2008). In Hong Kong, surveillance data from 2004 and 2005 at a tertiary care hospital revealed the incidence of VAP to be 10.6 per 1,000 ventilator days (Chawla, 2008). One study from China reported the incidence of VAP to be 1 per 1,000 ventilator days (Chawla, 2008). The number of NP for HAP in cases not intubated in our study were lower than those reported from other countries in Asia. The incidences of HAP in 2008 and 2009 in our hospital were 0.7 and 0.55 per 1,000 hospital days, respectively. Comparatively, the respective incidences were 18, 6.3, 6.0 and 1.0 per 1,000 admissions in Indian (Merchant *et al*, 1998), Korea (Kim *et al*, 2000), the Philippines and China study (Chawla, 2008).

Gram-negative bacteria were more commonly isolated in NP patients than gram-positive bacteria in our study. This finding is similar to other tertiary care hospitals in Thailand (Saenghirunvattana *et al*, 1994; Werarak *et al*, 2010). Among gram-negative organisms, *P. aeruginosa* was the most common cause

Table 7
Drug sensitivities among *K. pneumoniae* and *K. pneumoniae* (ESBL-producing) isolates from sputum cultures in 2008 and 2009.

Antimicrobial	*K. pneumoniae*				*K. pneumoniae* (ESBL)			
	2008		2009		2008		2009	
	n	% S	*n*	% S	*n*	% S	*n*	% S
Amikacin	334	99.1	302	98.7	384	86.5	398	87.7
Gentamicin	327	96.3	301	96.7	381	31.8	394	27.7
Netilmicin	8	87.5	12	75	346	68.5	368	71.7
Cephalotin	333	91.9	296	90.5	384	0	389	0
Cefotaxime	335	97.6	301	98	384	0	398	0
Ceftazidime	330	97.9	302	98.7	380	0	398	0
Cefoperazone/subactam	10	60	10	60	375	53.3	398	47
Ampicillin	334	0	303	0.3	383	0	398	0
Ampicillin/sulbactam	10	20	9	0	383	9.7	397	5.8
Piperacillin/tazobactam	10	60	11	54.5	366	52.2	381	34.6
Ofloxacin	326	94.8	301	95.3	377	44	391	39.4
Levofloxacin	319	95	272	94.9	346	46.5	339	43.7
Ciprofloxacin	10	40	10	40	383	31.3	397	26.4
Imipenem	13	100	10	100	384	99.7	398	99.7
Meropenem	10	100	10	90	383	99.5	398	100
Ertapenem	10	100	7	85.7	376	98.7	392	99
Cotrimoxazole	333	88.3	302	87.4	383	17.8	394	21.8
Tigecycline	9	66.7	10	50	378	70.1	370	64.6
Colistin	-	-	-	-	2	100	1	100

% S, percent of isolates sensitive to tested antimicrobial.

Table 8
Drug sensitivities among *S. aureus* isolates from sputum cultures in 2008 and 2009.

Antimicrobial	*S. aureus*			
	2008		2009	
	n	% S	*n*	% S
Cephalotin	635	46.8	665	50.7
Oxacillin	636	47	677	51
Clindamycin	634	44.2	674	49.3
Fosfomycin	626	92.8	482	89
Fusidic acid	623	94.9	636	89.8
Vancomycin	635	100	657	100

% S, percent of isolates sensitive to tested antimicrobial.

of HAP and *A. baumannii* was the most common cause of VAP. *P. aeruginosa*, *A. baumannii* and *K. pneumoniae* remained the three most commonly isolated pathogens among HAP and VAP patients in our study. The incidences and causative agents did not change between 2008 and 2009, but the rates resistance increased among multidrug-resistant (MDR) *P. aeruginosa*, MDR *A. baumannii*, extended spectrum β-lactamase-producing (ESBL) *K. pneumoniae* and methicillin-resistant *S. aureus*. The emergence of resistant microorganisms has a significant impact on treatment outcomes and poses a challenge to healthcare.

These findings differ from those in the United States and other Western countries, where gram-positive organisms, especially methicillin-resistant *S. aureus*, play a major role in HAP and VAP (Torres *et al*, 2009; Jones, 2010). Empiric treatment of HAP and VAP in Asia requires covering gram-negative pathogens and drug-resistant pathogens, more than gram-positive pathogens (Song *et al*, 2008). The causative agents of HAP and VAP are similar throughout Asia (Weber *et al*, 2007; Jones, 2010; Werarak *et al*, 2010). Data from Asian countries reveals two prominent trends (Chawla, 2008). First, *Acinetobacter* spp is an emerging cause of NP in several countries (including Thailand, Malaysia, Pakistan, and India), where it is one of the most common pathogens isolated in cases of HAP and VAP (Chawla, 2008). In Taiwan, it is the second most common pathogen causing NP (Chawla, 2008). But in China and Philippines, *P. aeruginosa* was the most common pathogen. Methicillin-resistant *S. aureus* (MRSA) is now the most common pathogen causing HAP and VAP in Korea and Taiwan, representing 80 - 90% of all *S. aureus* isolates in Korea and 73% in Taiwan, similar to those reported in international data (ATS and IDSA, 2005; Chawla, 2008).

In Thailand, *A. baumannii* was found in 28.2% of isolates from patients with HAP and VAP, followed by *P. aeruginosa* (17.8%), *Klebsiella* spp (7.7%), MRSA (7.6%), and *E. coli* (2.8%) (Chawla, 2008). Most of the isolates were multidrug-resistant bacteria (Chawla, 2008). Striking findings from the National Antimicrobial Resistance Surveillance Thailand (NARST) report for the year 2000 - 2005 included the emergence of pandrug-resistant (PDR) *A. baumannii*, carbapenem resistance increasing from 2.1% in 2000 to 46.7% in 2005, and cefoperazone/sulbactam resistance increasing from 3% in 2000 to 12% in 2005 (Apisarnthanarak *et al*, 2009). *P. aeruginosa* resistance to ceftazidime was high, ranging from 24.6 - 27.4% in NARST report. The average prevalence of multidrug (MDR) *P. aeruginosa*, *ie,* resistance to amikacin, ciprofloxacin and ceftazidime, was 33 - 44.6% in the NARST report. The antimicrobials with the greatest sensitivity rates among (MDR) *P. aeruginosa* isolates included netilmicin (88 - 90.8%), piperacillin/tazobactam (84.7 - 92.2%), cefoperazone/sulbactam (85.1 - 89.5%), imipenem (84.6 - 87.2%) and meropenem (84.5%) (Dejsirilert *et al*, 2009). The prevalence of ESBL-producing *K. pneumoniae* isolates ranged from 30.9% in 2000 to 39.2% in 2005 (Polwichai *et al*, 2009). During the same period, MRSA comprised 24 - 27% of all *S. aureus* isolates, and vancomycin resistance among MRSA isolates ranged from 0.1 - 0.8% (Mootsikapun *et al*, 2009).

Acinetobacter baumannii is a common cause of NP, especially VAP, in Thailand (Keerasuntonpong *et al*, 2006; Chaladchalam *et al*, 2008; Aimsaad *et al*, 2009) and other Asian countries (Torres *et al*, 1994). A study from Phramongkutklao Hospital, Bangkok conducted between January

and March 2008 found PDR *A. baumannii* (resistant to all tested antibiotics except colistin and tigecycline) comprised 67.5% of isolates and MDR *A. baumannii* comprised 21.1% of isolates. Resistance to carbapenems was detected in 84.2% of isolates but all *A. baumannii* isolates (100%) were sensitive to colistin and tigecycline (Aimsaad *et al*, 2009). In our study, *A. baumannii* isolates trended to be resistant to commonly used antimicrobial therapy for HAP and VAP, such as meropenem, imipenem, cefoperazone/sulbactam, and piperacillin/tazobactam. The only two antimicrobial agents still active against *A. baumannii* isolates in our study were colistin and tigecycline. Colistin, an older antimicrobial agent, has re-emerged as a an important therapeutic option giving excellent *in vitro* activity; numerous studies have confirmed its efficacy in serious infection, including VAP, with an acceptable safety profile (Michalopoulos and Karatza, 2010). Tigecycline is a promising therapeutic option for multidrug resistant *A. baumannii*, although more clinical data about its efficacy, especially in pulmonary infections, is required (Garnacho-Montero and Amaya-Villar, 2010).

Only half of *P. aeruginosa* isolates in our study were sensitive to ceftazideme; those same isolates were sensitive to piperacillin/tazobactam, netilmycin and colistin, but were less sensitive to carbapenem. The incidences of *P. aeruginosa* resistance to ceftazidime in Asia ranges from 12.9 to 35% and to imipenem from 9.7 to 30% (Lagamayo, 2008). ESBL-producing *K. pneumoniae*, which are not sensitive to third generation cephalosporins, but sensitive to carbapenem, were found in nearly half the isolates in our study. This finding is higher than the NARST report for 2000 to 2005 (Polwichai *et al*, 2009). Even though *S. aureus* was not the most common cause of HAP and VAP in Thailand, nearly half of *S. aureus* isolates in our study were MRSA, higher than previous surveillance data.

The treatment of HAP and VAP in Asian countries differs from that in the United States and other Western countries (ATS and IDSA, 2005; Song *et al*, 2008; Torres *et al*, 2009; File, 2010). The predominant pathogens in Asian countries are *A. baumannii*, *P. aeruginosa* and *K. pneumoniae*, but in the United States and other Western countries it is MRSA. Most of the gram-negative pathogens found in our study were multidrug resistant and some were pandrug resistant, which affects empiric therapy, cost and outcomes. The causative organisms for VAP tend to be more resistant than HAP; therefore, higher potential antimicrobials to cover drug resistance organisms were recommended (Song *et al*, 2008). Fourth generation cephalosporin, *eg*, cefepime or cefpirome, was preferred over ceftazidime as initial empiric treatment of agent for early-onset VAP. Other alternative antibiotics were imipenem, meropenem or piperacillin/tazobactam, and should be used in combination with aminoglycosides or fluoroquinolones. For late-onset VAP, carbapenems or piperacillin/tazobactam are preferred over third or fourth generation cephalosporins because these have greater activity against the ESBL producing gram-negative bacilli, Pseudomonas and Acinetobacter (Song *et al*, 2008). Piperacillin/tazobactam does not induce ESBL production in gram-negative bacteria, unlike cefepime (Song *et al*, 2008). Antibiotic regimens containing sulbactam compound (*eg*, cefoperazone/sulbactam and ampicillin/sulbactam) are especially recommended to treat MDR *Acinetobacter* spp in some Asian countries (Song *et al*, 2008). They were also recommended for

use in combination with aminoglycosides or fluoroquinolones (Song *et al*, 2008). For aminoglycosides, amikacin is preferred over gentamicin, and netilmycin had broad antimicrobial activity against aerobic gram-negative bacilli, including *Acinetobacter* strains.

The recommended treatment for MDR pathogens in Asia are as follows (Song *et al*, 2008): for MDR *P. aeruginosa*, the drugs of choice are piperacillin/tazobactam or carbapenems with or without aminoglycosides or fluoroquinolones (ciprofloxacin), and the second choice is polymyxin B or colistin with or without ciprofloxacin; for MDR Acinetobacter, the drugs of choice are cefoperozone/sulbactam and/or tigecycline, and the second choice is polymyxin B or colistin; for ESBL-producing *K. pneumoniae*, the drugs of choice are carbapenems or tigecycline, and the second choice is piperacillin/tazobactam. For MRSA, the drugs of choice are vancomycin or teicoplanin, and the second choice is linezolid or tigecycline.

Due to high incidences of HAP and VAP found in our study and the high resistance rates among isolates, the cost of treating NP was also high. The cost of treating NP is higher than treating other nosocomial infections (Inan *et al*, 2005). We recommend the use of appropriate initial empirical antibiotic therapy and then adjustment based on culture results. Infection control measures and education of healthcare workers are important to prevent HAP and VAP in critically ill and intensive care patients. In addition to high antibiotic cost, lengths of hospital stays and mortality rates are also increased in NP cases (Parker *et al*, 2008; Safdar *et al*, 2009).

In conclusion, our finding showed HAP and especially VAP, had high incidences and impact the cost of treatment of all nosocomial infections. The multidrug resistant gram-negative pathogens, *eg*, *A. baumannii*, *P. aeruginosa* and *K. pneumoniae*, were the major causative agents for NP in our study. Commonly used empiric antimicrobial therapy had less efficacy against these pathogens. The isolates in our study were less resistant to colistin and tigecycline. Due to the high cost of treatment, effective preventive measures are of vital importance.

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