Bacterial Aetiology and Antibiotic Susceptibility Patterns of Ventilator-Associated Pneumonia in Patients Admitted to the Intensive Care Unit at Sungai Buloh Hospital

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CONCLUSIONS: The microbiological data obtained from this study which summarises the common bacterial aetiology of VAP and their antibiotic susceptibility patterns; can be used to guide clinicians in the management of patients with VAP. The pitfalls in using empiric antibiotics for suspicion of VAP are the potential for antibiotic overuse, emergence of resistance, unnecessary adverse effects and potential toxicity. The major goals of VAP management are early and, appropriate antibiotics in adequate doses followed by de-escalation based on microbiological culture results and the clinical response of the patient. Antimicrobial stewardship program involving pharmacists, physicians and other healthcare providers optimize antibiotic selection, dose, and duration to increase efficacy in targeting causative pathogens and allows for the best clinical outcome. Better knowledge of local patterns of pathogens causing VAP can help facilitate treatment choices.

ABSTRAK

LATAR BELAKANG: Ventilator associated pneumonia (VAP) adalah jangkitan nosokomial yang sering berlaku di Unit Rawatan Rapi (ICU). VAP adalah jangkitan yang sering terjadi pada pesakit ICU lebih daripada 48 jam selepas intubasi endotrakeal dan pernafasan mekanikal. Walaupun ada kemajuan dalam ubat-ubatan, penjagaan rapi, dan pelbagai langkah-langkah pencegahan, VAP tetap menjadi penyebab utama morbiditi, kematian serta peningkatan kos. Patogen yang menjadi penyebab VAP mungkin berbeza-beza bergantung kepada negara, rantau dan hospital. Walau bagaimanapun, data tempatan mengenai etiologi bakteria dalam VAP masih kurang **OBJEKTIF**: Kajian ini bertujuan untuk mengkaji epidemiologi patogen bakteria yang menyebabkan VAP di Unit Rawatan Rapi Hospital Sungai Buloh. **KAEDAH**: Kajian retrospektif deskriptif telah dilakukan terhadap semua pesakit VAP di Hospital Sungai Buloh dari Januari 2012 sehingga Disember 2014. Semua data tersebut telah dikaji semula setelah diextrak daripada sistem maklumat (EHIS) Hospital Sungai Buloh.

KEPUTUSAN: Keputusan kajian mendapati mereka yang berumur di antara 36-59 tahun, jantina lelaki dan kaum Melayu adalah golongan majoriti pesakit VAP. Sebahagian besar pesakit VAP mempunyai sejarah pendedahan awal terhadap antibiotik dan pembedahan. *Acinetobacter* spp. (33%) adalah patogen yang paling tinggi dan 83.9% daripadanya adalah multi-drug resistant (MDR). Semua *Pseudomonas aeruginosa* adalah sensitif terhadap amikacin, gentamicin, cefepime, piperacillin-tazobactam, ciprofloxacin dan doripenem. Kebanyakan Enterobacteriaceae adalah sensitif terhadap kebanyakan antibiotik yang diuji termasuk cephalosporins. Sebanyak 75% daripada *Staphylococcus aureus* adalah methicillin-resistant *Staphylococcus aureus*

KESIMPULAN: Data Mikrobiologi dari kajian ini memberi kesimpulan tentang bakteria beserta dengan antibiotic yang sensitif terhadapnya, Oleh itu ia boleh digunakan sebagai panduan terapi antibiotik bagi kes VAP di unit rawatan rapi, Hospital Sungai Buloh. Antibiotik empirikal untuk kes VAP akan menyebabkan penggunaan antibiotik secara berlebihan, berlakunya resistan dan kesan sampingan yang tidak diingini. Matlamat utama dalam rawatan kes VAP adalah pengesanan awal, penggunaan antibiotik yang betul dan diikuti dengan pengubahsuaian yang sepatutnya berdasarkan kepada keputusan kultur mikrobiologi dan keadaan pesakit. Program pengawasan antimikrobia yang melibatkan ahli farmasi, doktor dan ahli kesihatan yang lain dapat mengoptimumkan pemilihan antibiotik, dos, dan tempoh penggunaan antibiotik. Ini untuk meningkatkan keberkesanan dalam menghapuskan patogen dan mendapatkan hasil klinikal yang terbaik. Pengetahuan serta data tempatan mengenai patogen yang menyebabkan VAP dapat membantu dalam pemilihan antibiotik yang tepat.

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LIST OF SYMBOLS AND ABBREVIATIONS

VAP	:	Ventilator-associated pneumonia
ICU	:	Intensive care units
ATS	:	American Thoracic Society
IDSA	:	Infectious Diseases Society of America
MDR	:	Multidrug-resistant
CNS	:	Coagulase-negative Staphylococci
MV	:	Mechanical ventilation
HIS	:	Hospital information system
BAL	:	Broncho-alveolar lavage
TA	:	Tracheal aspirate
CLSI	:	Clinical and Laboratory Standards Institute
USA	:	United States of America
CRE	:	Carbapenem-resistant Enterobacteriaceae
ESBL	:	Extended-spectrum beta-lactamase
MRSA	:	Methicillin-resistant *Staphylococcus aureus*
MSSA	:	Methicillin-sensitive *Staphylococcus aureus*
MDRO	:	Multidrug-resistant organism

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CHAPTER 1: INTRODUCTION

1.1 GENERAL INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection diagnosed in the intensive care units (ICU). VAP is an infection that occurs in an ICU patient more than 48 hours after endotracheal intubation and mechanical ventilation. Despite recent advances in antimicrobial therapy, better supportive care, and a wide range of prevention measures, VAP remain significant causes of patient morbidity and mortality as well as health care costs (Guillamet et. al., 2015).

Aetiologic agents worldwide causing VAP includes a wide spectrum of bacteria. Over the past 20 years, there has been a dramatic increase in health care-associated respiratory infections due to antibiotic-resistance or multidrug resistant pathogens (ATS, IDSA, 2005 & 2016). Bacteria causing VAP may originate from the patient's endogenous flora, other patients, hospital staff, contaminated devices, or the inanimate environment (Safdar et. al., 2005).

The type of organism that causes VAP usually depends on the duration of mechanical ventilation. In general, early VAP is caused by pathogens that are sensitive to antibiotics, whereas late onset VAP is caused by multi-drug resistance and more difficult to treat bacterial strain. However, this is by no means a rule and merely a guide to initiate antibiotic therapy until further clinical information is available (Gedik et. al., 2010).

Typically, bacteria causing early-onset of VAP include *Streptococcus pneumoniae* (as well as other *Streptococcus* species), *Haemophilus influenzae*, methicillin-sensitive *Staphylococcus aureus*, antibiotic-sensitive enteric Gram-negative

bacilli, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Proteus* spp. and *Serratia marcescens*. Culprits of late VAP are typically multidrug resistant (MDR) bacteria, such as methicillin-resistant *S. aureus*, *Acinetobacter* spp., *Pseudomonas aeruginosa*, and extended-spectrum beta-lactamase producing bacteria (Hunter, 2012). Commonly found bacteria in the oropharynx can attain clinically significant numbers in the lower airways. These bacteria include *Streptococcus viridans*, *Corynebacterium* spp., coagulase-negative staphylococci (CNS) and *Neisseria* spp. Frequently, VAP is due to polymicrobial infection. VAP from fungal and viral causes has a very low incidence rate, especially among the immunocompetent host (IDSA, 2005).

The exact prevalence of MDR organisms is variable between institutions and also within institutions (IDSA, 2005). Patients with a history of hospital admission for ≥ 2 days in the past 90 days, nursing home residents, patients receiving chemotherapy or antibiotics in the last 30 days and patients undergoing hemodialysis at outpatient centers are found to be more susceptible to drug resistant bacteria (IDSA, 2005; Hunter, 2012).

The causative pathogens of VAP may vary depending on the country, region and hospital. This study was conducted at Hospital Sungai Buloh which is a major tertiary hospital that receives referrals from district hospitals all over Klang Valley. Data on the local causative pathogens of VAP and their antibiotic susceptibility patterns can help guide appropriate antibiotic therapy, thereby improving patient prognosis and reducing mortality. Knowledge of the local incidence of VAP, associated risk factors and common pathogens causing VAP can also help in the development of effective preventive measures, which in turn will decrease the mortality and morbidity rates as well as duration of treatment and hospital stay that are commonly associated with VAP.

1.2 AIMS:

To study the epidemiology of bacterial pathogens causing ventilator-associated pneumonia in patients admitted to the intensive care unit at Hospital Sungai Buloh.

1.3 SPECIFIC OBJECTIVES

i. To determine the aetiological agents causing bacterial ventilator-associated pneumonia.

ii. To determine the antimicrobial susceptibility patterns of bacterial pathogens that cause ventilator-associated pneumonia.

iii. To identify related risk factors in patients with ventilator-associated pneumonia.

1.4 PROBLEM STATEMENT

Incorporation of local antibiotic susceptibilities is essential in monitoring the effectiveness of empirical antibiotic regimens in suspected VAP. This is extremely important as bacterial susceptibilities to antibiotics can vary by location. No specific empirical antibiotic regimen to date has been found to be superior, so selection should be based on local antibiotic susceptibility patterns.

1.5 RESEARCH QUESTIONS

i. What is the most common bacterial pathogen isolated in VAP patients admitted to the intensive care unit at Hospital Sungai Buloh?

ii. What is the antibiotic susceptibility pattern of each pathogen especially the most common pathogen isolated?

iii. Is an underlying medical illness an important risk factor for VAP?

CHAPTER 2: LITERATURE REVIEW

VAP is defined as pneumonia that occurs 48 hours or more after endotracheal intubation or tracheostomy, caused by infectious agents not present at the time when mechanical ventilation started. It is characterized by the presence of a new or progressive infiltrate, signs of systemic infection (fever, altered white blood cell count), changes in sputum characteristics, and detection of a causative agent. In newly published ATS, IDSA 2016 document, the term "hospital-acquired pneumonia (HAP)" will denote episodes of pneumonia that are not associated with mechanical ventilation. Thus, HAP and VAP patients henceforth will belong to 2 mutually exclusive groups.

VAP can be further divided into two types: (i) early-onset VAP which is defined as VAP that occurs within the first 4 days of ventilation, and (ii) late-onset VAP which is defined as VAP that occurs more than 4 days after initiation of mechanical ventilation (IDSA, 2005). In addition, it has been reported that mortality increases if an early antibiotic treatment is not provided to patients with VAP. Onset of VAP in most Ministry of Health (MOH) centers has been documented to occur after 5 days of ventilation, indicating that the VAP cases in MOH ICUs were mostly of late onset (MRIC, 2012).

Despite advances in antimicrobial therapy, better supportive care modalities and use of a wide range of preventive measures, VAP continues to be an important cause of morbidity and mortality in many ICUs around the world. VAP is associated with significant morbidity and mortality in the intensive care units (ICU) in Western and Asian countries, including Malaysia (Katherason et. al., 2008).

Clinical diagnosis for VAP lacks sensitivity and specificity, leading to both overdiagnosis and underdiagnosis of the condition. Routine bedside evaluation coupled with radiographic information provides suggestive but not definitive evidence that VAP is present or absent. Given the severity of VAP and the frequency of serious conditions that can mimic VAP, clinicians should be ready to consider additional tests that provide further evidence for VAP or that can help establish another diagnosis (Klompas, 2007).

Because of this lack of sensitivity and specificity, it is good practice to obtain microbiological samples of lower repiratory tract secretions before an antibiotic regime is started. Samples can be obtained invasively or non-invasively. Invasive sampling methods include bronchoalveolar lavage, protected specimen brushing and non-bronchscopic bronchoalveolar lavages. For non invasive sampling, it can be obtained from endotracheal aspirates.

The relative benefits of non-invasive and invasive techniques for obtaining samples and differentiating between airway colonisation and true infection are still vague. Although one study showed a reduction in mortality when an invasive diagnostic strategy was used (Fagon et. al., 2000), five other trials found no differences in hospital mortality, length of stay, or duration of mechanical ventilation when compared with cultures of endotracheal aspirates (Muscedere et. al., 2008).

Tracheal aspirates have a definite role to play in the management of VAP, but only when it is correctly correlated with clinical findings (Grossman & Fein, 2000). The use of quantitative results may be associated with the under-diagnosis of VAP, leading to inappropriate changes to antibiotic regimens and, in some cases, antibiotic delay or

withdrawal. Goel et al., (2012) in one study showed that quantitative culture of endotracheal aspirates is a useful test for the early diagnosis of VAP.

Quantitative cultures of tracheal aspirates have shown increased specificity when compared with qualitative analysis for the diagnosis of VAP. The sensitivity values for quantitative cultures of tracheal aspirates are significantly lower than those for qualitative cultures for VAP diagnosis in severely ill patients that have been receiving prior antibiotics therapy (Camargo et. al., 2004). Therefore, quantitative cultures of tracheal aspirates should not replace qualitative cultures for the purpose of confirming a clinical diagnosis of VAP or adjusting antimicrobial therapy. In addition, new IDSA 2016 guidelines suggest noninvasive sampling with semi-quantitative cultures to diagnose VAP, rather than invasive sampling with quantitative cultures and rather than noninvasive sampling with quantitative cultures.

Once specimens are obtained, the sample is sent for gram stain, culture and sensitivity. The Gram stain can provide crucial initial clues to the type of organism(s) and whether or not the material is purulent (defined as $\geq$ 25 neutrophils and $\leq$ 10 squamous epithelial cells per low power field. Culture results can be reported as semi-quantitative and/or quantitative values. Semiquantitative values obtained by endotracheal sampling are considered positive when the agar growth is moderate (+++) or heavy (++++), while quantitative positivity is defined as $\geq 10^5$ cfu/ml. Exact speciation of pathogen bacteria and their sensitivity to antibiotics can take a few days, but it helps provides invaluable information for definitive treatment of VAP (IDSA, 2005).

Aetiological agents widely differ according to the population of the patients in the intensive care unit, duration of stay and prior antimicrobial therapy. The bacteriological approach for the management of VAP avoids the problem of overtreatment by separating the colonizers from true infecting pathogens.

Gram-negative bacteria have emerged as the major group of pathogen causing VAP. Gadani, et. al., (2010) in their study, found that the most common organism associated with VAP is *Pseudomonas* spp. (43.24%), followed by *Klebsiella* spp. (18.91%). In another study (Chastre & Fagon (2002), the isolation of *Pseudomonas* spp. ranges from 15 to 25%. In Malaysia, Gram-negative organisms have accounted for a high majority (87.2%) of the causative organisms isolated from VAP patients. Over the last 7 years, *Acinetobacter* spp., *Klebsiella* spp. and *Pseudomonas* spp. were found to be the leading causative organisms of VAP, accounting for 44.4% of all organisms isolated. Methicillin-resistant *Staphyloccus aureus* accounted for 38.7% of all *Staphylococcus aureus* isolated (MRIC, 2012).

Over the years, the carbapenem group of antibiotics has emerged as one of the important antibiotics used in critically ill patients. There have been reports of increased occurrence of infection by carbapenem-resistant bacteria in health care settings in recent times (Thakuria et. al., 2013).

According to the new definition of drug resistance organism by the European Centre for Disease Prevention and Control (ECDC) and the Center for Disease Control and Prevention (CDC), MDR is defined as resistance to at least three classes of antibiotics (Magiorakos et al, 2012). The main classes are cephalosporins, aminoglycosides, fluoroquinolones, carbapenems and beta-lactam/beta-lactamase

inhibitors. Fifty eight percent of the causative organisms in VAP were MDR strains. *Acinetobacter* spp., *Klebsiella* spp. and *Pseudomonas* spp. constituted about 84.3%, 66.6% and 36.6% of the multi-drug resistant strains respectively. VAP caused by MDR *Acinetobacter baumannii* (MDR-AB) is shown to be related to high morbidity and mortality in healthcare settings (Özgür et al, 2014).

Antibiotic management is one of the important aspects in managing VAP cases. The clinician should base therapy on recent published guidelines and local antibiograms. An updated local antibiogram for each hospital and each ICU based on local bacteriological patterns and susceptibilities is essential to guide an optimally dosed initial empiric therapy. With any empiric antibiotic regimen, de-escalation is the key to reducing emergence of resistance.

The major goals of VAP management are early, and appropriate antibiotics in adequate doses followed by de-escalation based on microbiological culture results and the clinical response of the patient (Kalanuria *et al*, 2014). Selecting the appropriate antibiotic depends on the duration of mechanical ventilation. Late onset VAP (> 4 days) requires broad spectrum antibiotics whereas early onset (≤ 4 days) can be treated with limited spectrum antibiotics.

The antibiotic spectrum refers to the range of microorganisms an antibiotic is usually effective against and is an important consideration for empiric therapy. Decision on choice of antibiotic based on the spectrum of coverage should be made based on severity of illness, pathogen probabilities (whether Gram-positive or Gram-negative bacteria), local resistance patterns, co-morbid conditions and recent antibiotic exposure.

Risk factors for MDR VAP have been addressed in several studies. Factors associated with an increased risk of MDR VAP is the use of intravenous antibiotics in the past 90 days, ≥5 days of hospitalization prior to the occurrence of VAP, septic shock at the time of VAP, acute respiratory distress syndrome (ARDS) before VAP, and renal replacement therapy prior to VAP.

In the absence of risk factors for multidrug-resistant bacteria, clinician should choose empirical therapy for *Streptococcus pneumoniae*, *Haemophilus influenzae*, methicillin-sensitive *Staphylococcus aureus*, and antibiotic-sensitive gram-negative enteric organisms. Antibiotic choices include ceftriaxone, quinolones (levofloxacin, moxifloxacin, or ciprofloxacin), or ampicillin/sulbactam. When risk factors for multidrug resistant organisms are present, clinician must consider not only the organisms listed above but also *Acinetobacter, Pseudomonas aeruginosa*, *Klebsiella*, *Enterobacter*, *Serratia*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, and methicillin-resistant *S. aureus*. Thus, empirical therapy is broadened to include an antipseudomonal cephalosporin (cefepime or ceftazadime), an antipseudomonal carbepenem (imipenem or meropenem), or a beta-lactam/beta-lactamase inhibitor (pipercacillin-tazobactam) plus linezolid or vancomycin.

In an effort to minimize patient's harm and limit exposure to unnecessary antibiotics and reduce the development of antibiotic resistance, IDSA recommends that the antibiogram data is utilized to decrease the unnecessary use of dual gram-negative and empiric methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotic treatment. The definitive choice of antibiotics should be made after the review of culture and susceptibility results and therapy should then be tailored accordingly (National Antibiotic guideline, 2008).

Inappropriate therapy and delayed initiation of appropriate therapy increased the mortality of ventilator-associated pneumonia. Patients with inappropriate therapy and/or delayed initiation of appropriate therapy had a more gradual increase in clinical pulmonary infection score than those receiving adequate therapy, and this increase was found to occur prior to the time of the clinical diagnosis (Luna et. al., 2006).

Antimicrobial stewardship programs involving pharmacists, physicians and other healthcare providers optimize antibiotic selection, dose, and duration to increase efficacy in targeting causative pathogens and allow the best clinical outcome.

CHAPTER 3: MATERIAL AND METHODS

3.1 ETHICS STATEMENT

This study involved retrospective review and analysis of bacterial pathogens of VAP cases which were isolated at the microbiology laboratory of Hospital Sungai Buloh. Specific written or verbal consent from patients was not required as the data used were obtained from the existing laboratory records and were used anonymously. No additional procedure or intervention was done to the patient.

3.2 STUDY DESIGN AND SETTING

This was a cross-sectional study conducted at Hospital Sungai Buloh, a 630-bedded tertiary hospital, which is also an infectious disease tertiary referral center. A retrospective analysis of data from ICU, medical records of patients and microbiology laboratory records of those who had been diagnosed with VAP from January 2012 to December 2014 was performed. Prevalence was assessed by identifying all documented VAP cases in ICU during the study period, and from those the proportion that were due to bacterial pathogens were then calculated.

3.3 DEFINITION OF PATIENT POPULATION AND EXCLUSION CRITERIA

The patient population was defined as all VAP patients in ICU at Hospital Sungai Buloh from January 2012 to December 2014, and the inclusion criteria included all patients aged 18 years old and above who were on mechanical ventilation (MV) for $\geq$ 48 hr. The paediatric group (below 18 years old) and duplicate samples were excluded from the study.

3.4 DATA COLLECTION AND DEFINITIONS OF THE VARIABLES USED

This is a retrospective study that involved analysis of secondary data. The data was reviewed using information system (HIS) of Hospital Sungai Buloh. All data were collected according to the patient's information sheet and included patient's demographic data, clinical history and result of investigations.

3.5 STUDY FLOW

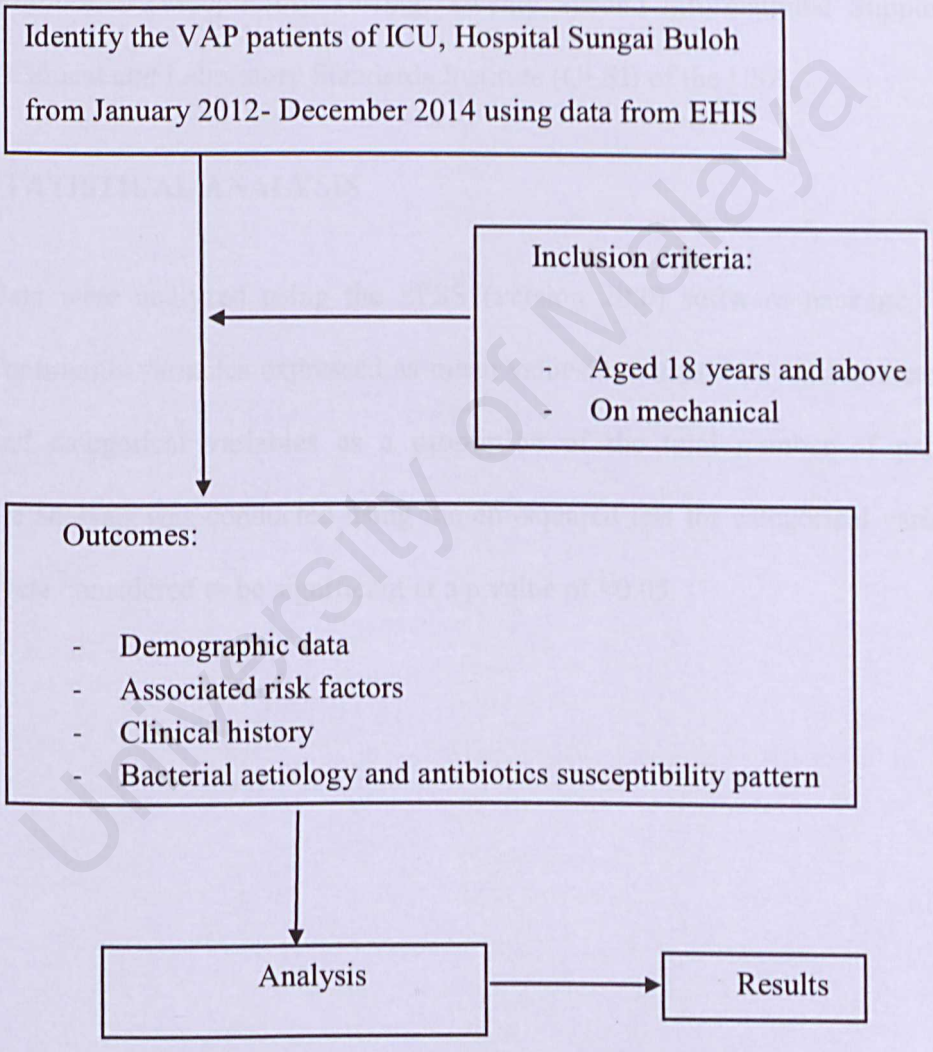

Figure 3.1: Flowchart of sampling process

3.6 MICROBIOLOGY LABORATORY PROCEDURES: BACTERIOLOGY AND ANTIMICROBIALS SUSCEPTIBILITY TESTING

Tracheal aspirate and broncho-alveolar lavage (BAL) isolates were identified by their classic phenotypic appearances on routine culture media and based on their biochemical profiles at the diagnostic bacteriology laboratory of Hospital Sungai Buloh. The antimicrobial susceptibility testing was determined by the Performance Standards for Antimicrobials Susceptibility Testing; Twenty Second Informational Supplement from the Clinical and Laboratory Standards Institute (CLSI) of the USA.

3.7 STATISTICAL ANALYSIS

Data were analyzed using the SPSS (version 20.0) software package (IBM, USA). Continuous variables expressed as mean values ± standard deviation, mean and range, and categorical variables as a proportion of the total number of patients. Univariate analysis was conducted using the chi-squared test for categorical variables. Factors were considered to be significant at a p value of <0.05.

CHAPTER 4: RESULTS

4.1 PREVALENCE

Table 4.1 Prevalence of VAP cases at ICU, Hospital Sungai Buloh

Year	Cases Number (n)	Percentage (%)
2012	30	31.9
2013	39	41.5
2014	25	26.6
Total	94	100.0

A total of 94 non-repeated cases of VAP were documented from January 2012 until December 2014 in Hospital Sungai Buloh. The highest VAP cases was recorded in 2013 (n=39, 41.5%) and lowest was seen in 2014 (n=25, 26.6%).

4.2 DESCRIPTION OF CASES

Table 4.2: Socio-demographic data and clinical characteristics of patients with VAP

Variable	Frequency	%
Age		
18-35	33	35.1
36-59	44	46.8
>=60	17	18.1
Gender		
Male	72	76.6
Female	22	23.4
Race		
Malay	56	59.6
Chinese	12	12.8
India	15	16.0
Others	11	11.7
Presence of underlying co-morbidity		
Yes	48	51.1
No	46	48.9
Previous antibiotic therapy		
Yes	76	80.9
No	18	19.1
Recent surgery		
Yes	71	75.5
No	23	24.5

The demographic and clinical characteristics are summarized in Table 4.2. Those between the ages of 36-59, male in gender and Malay in race comprised the majority of the patients with VAP. A high proportion of VAP patients had previous antibiotic exposure and recent surgery (n=76, 80.9% and n=71, 75.5%). However, there was no obvious difference between patient with and without underlying co-morbidities.

Table 4.3: Types of respiratory specimens tested for culture and sensitivity

Type of sample	N= 94 (%)
Tracheal aspirate	84 (89.4)
Broncho-alveolar lavage	10 (10.6)

Table 4.4: Initial Gram-stained smear results of respiratory specimens

Gram stain	N=94 n	%
Gram-positive	5	5.3
Gram-negative	89	94.7

n (%), number and percentage of patients

The majority of respiratory specimens received were tracheal aspirate (n=84, 89.4%) as shown in table 4.3. A higher proportion of Gram-negative organisms were seen on initial smear of the respiratory specimens (Table 4.4).

Table 4.5 Distribution of bacterial pathogens isolated from patients with VAP

Bacterial aetiology	n	%
Acinetobacter spp.	31	33.0
Enterobacteriaceae	19	20.2
Pseudomonas aeruginosa	20	21.3
Staphylococcus spp.	4	4.3
Chryseobacterium spp.	1	1.1
Stenotrophomonas maltophilia	1	1.1
Mixed growth	16	17.0
No pathogen isolated	2	2.1

n (%), number and percentage of patients

Table 4.6 Distribution of bacterial pathogens among Enterobacteriaceae isolates

Enterobacteriaceae	(N=19) n	%
K.pneumoniae CRE[a]	1	1.1
K. pneumoniae ESBL[b]	6	6.4
E.coli[c] ESBL	1	1.1
K. pneumoniae[d]	9	9.6
Enterobacter spp.	2	2.1

n (%), number and percentage of patients

[a] *CRE, carbapenem-resistant* Enterobacteriaceae;

[b] *ESBL, extended-spectrum beta-lactamase;*

[c] *E. coli, Escherichia coli;*

[d] *K. pneumoniae, Klebsiella pneumoniae*

Table 4.7 Distribution of methicillin-sensitive and methicillin-resistance strains among *Staphylococcus aureus* isolates

Staphylococcus aureus	(N=4) n	%
MRSA[a]	3	3.2
MSSA[b]	1	1.1

n (%), number and percentage of patients

[a] *MRSA, methicillin-resistant Staphylococcus aureus;*

[b] *MSSA, methicillin-sensitive Staphylococcus aureus*

Table 4.8 Distribution of MDR and nonMDR strains among *Acinetobacter* isolates

MDR *Acinetobacter*	(N=31) n	%
Yes	26	83.9
No	5	16.1

n (%), number and percentage of patients

According to Table 4.5, *Acinetobacter* spp. was the common cause of VAP (n=31, 33%) followed by *Pseudomonas aeruginosa* (n=20, 21.3%) and Enterobacteriaceae (n=19, 20.2%). *K. pneumoniae* was the most isolated species among the Enterobacteriaceae as shown in table 4.6. Only 1.1% (n=1) CRE case while ESBL cases reported as 7, 7.5% (Table 4.6).

In Table 4.7, MRSA was the commonest isolated among the *Staphylococcus aureus* (n=3, 3.2%) isolates and 26 out of 31 isolates of *Acinetobacter* spp., were MDR (Table 4.8).

4.3 ANTIMICROBIAL SUSCEPTIBILITY PROFILES OF THE ISOLATES

Table 4.9 Antimicrobial susceptibility profiles among Enterobacteriaceae

Antibiotic tested	Enterobacteriaceae isolates (N=19)		
	Non-ESBL[a] N= 11 n(%)	ESBL N=7 n(%)	CRE[b] N=1 n(%)
SAM[c]	10 (90.9)	0	0
AMC[d]	9 (81.8)	0	0
TZP[e]	11 (100)	3(42.9)	0
CXM[f]	10 (90.9	0	0
CRO[g]	11 (100)	0	0
CAZ[h]	11 (100)	0	0
CTX[i]	11 (100)	0	0
FEP[j]	11 (100)	2(28.6)	0
CIP[k]	11(100)	1(14.3)	0
SXT[l]	11 (100)	1(14.3)	0
CN[m]	11(100)	6(85.7)	0
AN[n]	11(100)	6(85.7)	1(100)
NET[o]	11(100)	6(85.7)	1(100)
ETP[p]	11(100)	7 (100)	0
IPM[q]	11 (100)	7 (100)	1(100)
MEM[r]	11 (100)	7 (100)	0
DOR[s]	11 (100)	7 (100)	0

n (%), number and percentage of patients; [a] ESBL, extended spectrum beta-lactamase; [b] CRE, carbapenem-resistant Enterobacteriaceae*; [c] SAM, ampicillin-sulbactam; [d] AMC, amoxicillin-clavulanic acid; [e] TZP, piperacillin-tazobactam; [f] CXM, cefuroxime; [g] CRO, ceftriaxone; [h] CAZ, ceftazidime; [i] CTX, cefotaxime; [j] FEP, cefepime; [k] CIP, ciprofloxacin; [l] SXT, trimethoprim-sulfamethoazole; [m] CN, gentamicin; [n] AN, amikacin; [o] NET, netilmicin; [p] ETP, ertapenem; [q] IPM, imipenem; [r] MEM, meropenem; [s] DOR, doripenem*

In Table 4.9, all non-ESBL-producing Enterobacteriaceae were sensitive to the third-generation cephalosporins (cefuroxime, ceftriaxone, ceftazidime and cefotoxime), fourth-generation cephalosporins (cefepime), aminoglycosides (amikacin and gentamicin), and the carbapenem (ertapenem, imipenem, meropenem and doripenem). The non-ESBL-producing isolates showed high susceptibility towards beta-lactam/beta-

lactamase inhibitors. All ESBL-producing Enterobacteriaceae were sensitive to carbapenem. None of the ESBL-producing Enterobacteriaceae isolates were susceptible to the third-generation cephalosporins. Only 42.9% (n=3) of the ESBL-producing Enterobacteriaceae were susceptible to piperacillin-tazobactam. Only one of the CRE isolate was resistant to ertapenem, meropenem and doripenem.

Table 4.10 Antimicrobial susceptibility profiles among *Pseudomonas aeruginosa*

Antibiotic tested	N=20	
	n	%
AN[a]	20	100
CN[b]	20	100
CAZ[c]	19	95
FEP[d]	20	100
TZP[e]	20	100
CIP[f]	20	100
MEM[g]	19	95
DOR[h]	20	100

n (%), number and percentage of patients

[a]AN, amikacin;[b]CN, gentamicin;[c]CAZ, ceftazidime;

[d]FEP, cefepime; [e]TZP, piperacillin-tazobactam;

[f]CIP, ciprofloxacin; [g]MEM, meropenem;

[h]DOR, doripenem

Table 4.10 showed all *Pseudomonas aeruginosa* isolates were susceptible to the aminoglycosides (amikacin and gentamicin), cefepime, piperacillin-tazobactam, ciprofloxacin and doripenem. The susceptibility of *P. aeruginosa* isolates towards ceftazidime and meropenem were 95% (n=19) as shown in table 4.10.

Table 4.11 Antimicrobial susceptibility profiles among *Acinetobacter* spp.

Antibiotic tested	Non-MDR[a] N=5 n(%)	MDR N=26 n(%)
SAM[b]	5(100)	0
TZP[c]	5(100)	0
CN[d]	5(100)	1(3.8)
AN[e]	5(100)	2(7.7)
CIP[f]	5(100)	0
CAZ[g]	5(100)	0
TIG[h]	5(100)	15(57.7)
IMP[i]	5(100)	0
MEM[j]	5(100)	0
DOR[k]	5(100)	0

n (%), number and percentage of patients

[a] MDR, multi-drug resistant; [b] SAM, ampicillin-sulbactam;

[c] TZP, piperacillin-tazobactam; [d] CN, gentamicin; [e] AN, amikacin;

[f] CIP, ciprofloxacin; [g] CAZ, ceftazidime; [h]TIG, tigecycline;

... [i] IPM, imipenem; [j] MEM, meropenem; [k] DOR, doripenem

Table 4.12 Antimicrobial susceptibility profiles among *Staphylococcus aureus* isolates

Antibiotic tested	N=4 n	%
FOX[a]	1	25
ERY[b]	1	25
CLIN[c]	2	50
CN[d]	3	75
FA[e]	4	100
RIF[f]	4	100
TEI[g]	3	75
TIGE[h]	2	50
SXT[i]	3	75
LINE[j]	4	100

n (%), number and percentage of patients

[a]FOX, cefoxitin; [b]ERY, erythromycin; [c]CLIN, clindamicin;

[d]CN, gentamicin; [e]FA, fucidic acid; [f]RIF, rifampicin;

[g]TEI, teicoplanin; [h]TIGE, tigecycline;

[i]SXT, trimethoprim-sulfamethoxazole; [j]LINE, linezolid

Based on Table 4.11, all non-MDR *Acinetobacter* isolates were susceptible to each of the antibiotics tested. All the MDR-*Acinetobacter* spp. isolates were not susceptible to each antibiotic tested except gentamicin (n=1, 3.8%), amikacin (n=2, 7.7%) and tigecycline (n=15, 57.7%). Results of the antimicrobial susceptibility profiles among *Staphylococcus aureus* isolates are shown in Table 4.12. Only one isolate was susceptible to cefoxitin (i.e. methicillin-sensitive) while the other 3 isolates were methicillin-resistant.

CHAPTER 5: DISCUSSION AND LIMITATIONS

5.1 DISCUSSION OF THE FINDINGS

5.1.1 Socio-demographic data and clinical characteristics

The majority of VAP patients were between the ages of 36-59, similar to the findings from a local study by Katherason,et.al., (2009). Charles et. al., (2013) reported a mean age of 47.8 among their patients. In other studies, the mean age was found to be more than 60 years (George et. al., 2010; Ranjan et. al., 2014). But in contrast, Gadani et. al., (2010) had reported a mean age of 34 years old.

In this study, men comprised the majority of patients, similar to findings found in other studies (Charles et. al., 2013, Katherason,et.al., 2009; Ranjan et. al., 2014; Gadani et. al., 2010). The predominant race was Malay which was similarly reported by another (Katherason,et.al., 2009) .

A high proportion of VAP patients had previous antibiotic exposure (n=76, 80.9%) and recent surgery (and n=71, 75.5%). This was similar to the findings in a study by Chawla (2008). It is known that use of broad-spectrum antibiotics is related with resistance (Falagas et. al., 2006). In addition, the use of carbapenems and third-generation cephalosporins appear to be related to the development of *A. baumannii* strains with an MDR phenotype.

In this study, there was no obvious difference between patients with and without underlying co-morbidity. This contradicts previous studies (Chawla, 2008) that states underlying of at least one co-morbidity is considered as risk factor for VAP.

5.1.2 Types of respiratory specimen

The majority of respiratory specimens tested were tracheal aspirates (89.4%). Quantitative cultures obtained by different methods, including BAL and TA seem to be fairly equivalent in diagnosing VAP (Reo-Neto et. al., 2008). However, new ATS/IDSA guideline suggest noninvasive sampling (tracheal aspirate) with semi-quantitative cultures to diagnose VAP, rather than invasive sampling (ie, BAL, protected specimen brush and blind bronchial sampling) with quantitative cultures and rather than noninvasive sampling with quantitative cultures (Kalil et. al., 2016). Tracheal aspirate is the most easiest to obtain because it does not require provider involvement compared to broncho-alveolar lavage which requires bronchoscopic guidance. Reduced costs and similar outcomes were reported using either quantitative or qualitative tracheal aspirates for guiding or deciding antibiotic treatment for VAP (Ruiz et. al., 2000).

5.1.3 Distribution of bacterial pathogens isolated from patients with VAP

Most cases of VAP are caused by bacterial pathogens that normally colonize the oropharynx and gut, or that are acquired via transmission by health-care workers from environmental surfaces or from other patients.

In this study, the main bacterial pathogens of VAP were caused by Gram-negative organisms (76.7%). This was also supported by the initial Gram-stained smears of respiratory specimens that mainly showed Gram-negative organisms (94.7%). These findings were similar to the findings from a few studies that reported that Gram-negative bacilli represented the majority (58%) of the isolates, while Gram-positive bacteria made up another 35% (Park, 2005; Restrepo et al., .2013; Ranjan et al., 2014 Thakuria et al., 2013). The rapid availability of cytological data, including inflammatory

cells and gram stains, may be useful in initial therapeutic decisions in patients with suspected VAP (Reo-Neto et al., 2008). The clinician will get some ideas regarding the aetiology of VAP that they are dealing with.

According to this study, *Acinetobacter* spp. was the main causative pathogen of VAP followed by *Pseudomonas aeruginosa*. This was similar to findings reported by Goel et al., (2012) and Balkhy et al., (2014). However, other studies (Chastre et al., 2002; Gadani et al., 2010), reported a predominance of *Pseudomonas aeruginosa* followed by *Acinetobacter* spp. among their VAP isolates.

The Enterobacteriaceae, or enteric Gram-negative bacilli, made up the third most common group of pathogens. Collectively, they accounted for 20.2% of the isolates. This group included roughly equal numbers of *Klebsiella* spp., *Escherichia coli*, and *Enterobacter* spp. The findings from this study were in contrast to those by Jakribettu et al., (2012) that showed *Klebsiella* spp. is the most frequent isolate in VAP.

Another different study (Woske et al., 2001) reported *Staphylococcus aureus* as the main bacterial pathogen of VAP. In our study, VAP caused by this organism comprised only 4.3%.

5.1.4 In-Vitro Antimicrobial Susceptibility Profiles for the Isolates

MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories (Magiorakos et al., 2012). As mentioned earlier, most *Acinetobacter* spp. isolates that caused VAP in this study were found to be MDR. They were resistant to most groups of antibiotics, including the carbapenems. *Acinetobacter* spp. has a propensity to rapidly develop resistance to multiple antimicrobial agents. In

one study showed *Acinetobacter* spp. has lower susceptibility to ampicillin, ceftriaxone, ceftazidime, gentamicin and kanamycin (Constantiniu et al., 2004).

All *Pseudomonas aeruginosa* isolates that caused VAP tested in this study were found to be sensitive to the antimicrobials tested. This was in contrast to the findings from one study reported that most strains of *Pseudomonas aeruginosa* were resistant to the commonly used beta-lactam antibiotics known to be effective against *Pseudomonas* spp. (Gupta et al., 2011).

In this study, the CRE rate was 1.1%, with one of the *Klebsiella pneumoniae* isolate showing susceptibility to only netilmicin, amikacin and imipenem. In a large multi-center study of CRE infections in Greek intensive care units, VAP due to CRE was the second most common infection after bacteremia and had a similar mortality as line-related bacteremia (Tedja et al., 2014). The global spread of carbapenem-resistant Enterobacteriaceae (CRE) is particularly concerning because limited treatment options remain for CRE. The increase incidence of carbapenemase production might be as a result of rampant use of carbapenem group of antibiotics and natural selection tool of bacteria like plasmid and chromosomal-mediated gene transfer among species of carbapenemase-producing Enterobacteriaceae. It is fast becoming a major health threat among ICU of developing countries.

Among the Enterobacteriaceae, majority of the isolates (n=11, 57.9%) were sensitive strains which showed susceptibility to amoxicillin-clavulanic acid (81.8%) and cefuroxime (90.9%). About 36.8% of Enterobacteriaceae isolates were ESBL-producers and all of these isolates were susceptible to carbapenem.

Staphylococcus aureus is a Gram-positive coccus that frequently colonizes the anterior nares and is consistently one of the most important causes of nosocomial infection and of VAP. Traditionally, most strains have been susceptible to beta-lactam antibiotics (methicillin-sensitive *S. aureus*), but a study has shown that the prevalence of methicillin-resistant *S. aureus* (MRSA) strains is increasing (Park, 2005). The finding is also similar in this study that showed 75% of *S. aureus* isolates were methicillin resistant. One previous study showed all strains of *S. aureus* were MRSA (Gupta et al., 2011). The likelihood that VAP due to *S. aureus* will be methicillin-resistant becomes nearly certain if the patient has received antibiotic treatment and the onset of VAP is later in the hospital course (Park, 2005).

5.2 LIMITATIONS

Although this study has reached its aims, there were some unavoidable limitations. Therefore, any conclusions drawn and recommendations offered will have to be made against these limitations.

5.2.1 Setting of the study

This study was conducted at Sungai Buloh Hospital which is a tertiary referral centre that serves sicker patients with more complex disease. Thus findings from this study may not be reflect or applicable to non-referral centers like the district or community-based hospitals in Malaysia.

5.2.2 Sample size and selection of variables for inclusion in the study

Another possible limitation of this study was the small sample size. A small number of patients with VAP made the result less conclusive to be inferred to the comparison of variables. The inclusion criteria in this study were based on the most commonly reported risk factors in previous study. Thus, there is a possibility that there are variables that were not included in this study that may also be the risk factors for VAP.

5.2.3 Study design

The study done was relied on secondary data (retrospective observational study). Information regarding patients' demographic and clinical characteristics was obtained from data recorded in the EHIS of Hospital Sungai Buloh which were recorded by the attending physicians. Therefore, the accuracy of the data collected could not be completely ascertained, although all efforts were taken to extract and interpret the data from these case notes as accurately as possible.

5.2.4 Potential bias encountered in the study

A relatively high number of patients had to be excluded from this study due to incomplete or missing medical case notes. Therefore, this may have given rise to some selection bias.

CHAPTER 6: CONCLUSIONS & RECOMMENDATIONS

6.1 CONCLUSIONS

This study concluded that the age group of 36-59 years was the most commonly associated with VAP. In addition, a high proportion of VAP patients had previous antibiotic exposure and recent surgery.

Acinetobacter spp. and *Pseudomonas aeruginosa* were the most common bacterial pathogens responsible for VAP from the data gathered at Sungai Buloh Hospital. The analysis of the susceptibility pattern revealed that the most *Acinetobacter* spp. causing VAP were MDR and the *Staphylococcus aureus* isolated were MRSA. This was contradicting with *Pseudomonas aeruginosa* isolates which were susceptible to most of anti-pseudomonal agents.

6.2 RECOMMENDATIONS

Microbiological data should be used for tailoring antibiotic therapy and not be restricted only to diagnosis. The pitfalls in using empiric antibiotics for the suspicion of VAP is the potential cause for antibiotic overuse, emergence of resistance, unnecessary adverse effects and potential toxicity. The major goals of VAP management are early, and appropriate antibiotics in adequate doses followed by de-escalation based on microbiological culture results and the clinical response of the patient. Antimicrobial stewardship programs involving pharmacists, physicians and other healthcare providers optimize antibiotic selection, dose, and duration to increase efficacy in targeting causative pathogens and allow for the best clinical outcome. Better knowledge of local patterns of pathogens causing VAP can help to facilitate treatment choices. Local data collected in more similar studies can assist in making informed treatment choices.

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APPENDIX A: DATA COLLECTION FORM

DATA COLLECTION FORM

Demographic data

Patient number : _____ Year:

Date of admission: _____ Date of discharge: _____

Age : _____

Gender ☐ Male ☐ Female

Race ☐ Malay ☐ Chinese ☐ India ☐ Other

Clinical history

Clinical Diagnosis: _____

Clinical presentation:

- Temperature : ☐ >38°C ☐ <36°C
- Shock ☐ Yes ☐ No
- White cell count ☐ $>10x10^5$ ☐ $< 4x10^5$
- Platelet count $<150x\ 10^3$ ☐ Yes ☐ No

Associated risk

Underlying medical illness:

☐ Diabetes mellitus

☐ Chronic renal disease

☐ Other (specify): _____

☐ No medical illness

Immunosuppression state:

☐ Human immunodeficiency virus

☐ Malignancy/ post transplantation; specify _____

☐ Cytotoxic drug

☐ Others; specify _____

Recent surgery: Yes ☐ No ☐

Previous antibiotic therapy: Yes ☐ No ☐

Result

Respiratory samples: ☐ Tracheal aspirate ☐ Broncho-alveolar lavage

Gram stain: ☐ Gram-positive ☐ Gram-negative

Bacterial aetiology:

Enterobacteriaceae	
Pseudomonas aeruginosa	
Acinetobacter spp.	
Staphylococcus spp.	
Others	

Antibiotic sensitivity pattern according to organism:

ii) Enterobacteriaceae

Antibiotic	Sensitive	Intermediate	Resistant
Ampicillin			
Cefoperazone			
Cefuroxime			
Gentamicin			
Cotrimoxazole			
Amikacin			
Ceftazidime			
Amoxicillin/clavulanate			
Cefotaxime			
Ciprofloxacin			
Imipenem			
Cefpodoxime			
Cefepime			
Sulbactam/cefoperazone			
Netilmicin			
Meropenem			
Piperacillin/tazobactam			
Ampicillin/sulbactam			
Ertapenem			
Doripenem			
Tigecycline			
Cefazolin			
Ceftaroline			

ii) *Pseudomonas aeruginosa*

Antibiotic	Sensitive	Intermediate	Resistant
Amikacin			
Amoxicillin/clavulanate			
Imipenem			
Gentamicin			
Ceftazidime			
Piperacillin/tazobactam			
Cefepime			
Ciprofloxacin			
Netilmicin			
Meropenem			
Doripenem			
Cotrimoxazole			
Polymyxin B			

iii) *Acinetobacter* spp.

Antibiotic	Sensitive	Intermediate	Resistant
Amikacin			
Ampicillin/sulbactam			
Gentamicin			
Sulbactam/cefoperazone			
Ceftazidime			
Augmentin			
Doripenem			
Meropenem			
Imipenem			
Ciprofloxacin			
Piperacillin/tazobactam			
Tigecycline			

iv) *Staphylococcus* spp.

Antibiotic	Sensitive	intermediate	resistant
Cotrimoxazole			
Gentamicin			
Fusidic acid			
Rifampicin			
Mupirocin			
Linezolid			
Cefoxitin			
Clindamycin			
Erythromycin			
Teicoplanin			
Tigecycline			
Ceftaroline			
Vancomycin			

Bacterial Aetiology and Antibiotic Susceptibility Patterns of Ventilator-Associated Pneumonia in Patients Admitted to the Intensive Care Unit at Sungai Buloh Hospital

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