EVALUATION OF SURVEILLANCE RESPIRATORY CULTURE IN PREDICTING NOSOCOMIAL PNEUMONIA PATHOGENS

DR SYAZWANI BT MOHD TAJUDIN

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PATHOLOGY (MICROBIOLOGY)

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LIST OF SYMBOLS/ ABBREVIATIONS

Symbols / Abbreviations	Meaning
n	Frequency
κ	kappa
%	Percentage
<	Less than
>	More than
=	Equal
ATS	American thoracic society
BAL	Broncho-alveolar lavage
CAP	Community-acquired pneumonia
CLSI	Clinical and Laboratory Standard Institute
CRE	Carbapenem Resistant *Enterobacteriaceae*
ETA	Endotracheal aspirate
ESBL	Extended-spectrum Beta-Lactamases
ETT	Endotracheal tube
HAI	Hospital-acquired infection
HAP	Hospital-acquired pneumonia
HUSM	Hospital Universiti Sains Malaysia
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IQR	Interquartile range
MDR	Multi-drug resistant
MRIC	Malaysian Registry of Intensive Care

MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
PP	Potential pathogen
SD	Standard deviation
TC	Tracheal/tracheobronchial colonization
VAP	Ventilator-associated pneumonia

ABSTRAK

Penilaian sampel saringan respiratori untuk meramal mikroorganisma penyebab pneumonia berkait dengan ventilator (VAP)

Pengenalan: VAP adalah salah satu penyebab utama morbiditi dan kematian bagi pesakit yang dirawat di Unit Rawatan Rapi (ICU). Ini adalah punca utama untuk peningkatan tempoh rawatan di hospital, jangkitan multi-drug resistant (MDR) mikroorganisma dan peningkatan kos hospital. Saringan sampel respiratori dilakukan terhadap pesakit yang dimasukkan ke ICU walaupun tidak terdapat tanda-tanda jangkitan paru-paru. Kepentingan saringan sampel tersebut untuk meramal mikrorganisma penyebab VAP masih tidak dapat dipastikan. Oleh kerana terdapat laporan yang bertentangan mengenai peranan saringan ini, terdapat keperluan untuk menilai semula peranannya dalam meramal mikroorganisma penyebab pneumonia berkait dengan ventilator (VAP).

Objektif: Untuk menilai kebolehpercayaan sampel saringan respiratori dalam meramal mikroorganisma penyebab VAP.

Metodologi: Ini adalah kajian prospektif yang dijalankan di ICU General Hospital Universiti Sains Malaysia, dari Julai 2017 hingga Disember 2018. Semua pesakit dewasa yang dimasukkan ke ICU beserta sampel saringan respiratori termasuk dalam kajian ini. Pesakit disusuli sehingga mereka dipindahkan dari ICU. Statistik Analisis Indeks Cohen Kappa(κ) telah digunakan untuk mengenal pasti kebolehpercayaan keputusan saringan respiratori dalam meramal mikroorganism penyebab VAP.

Keputusan: Sebanyak 193 pesakit yang dimasukkan ke dalam kajian ini. 88/193 (46%) pesakit mempunyai keputusan saringan positif. Daripada 63/193 (32.6%) pesakit diambil sampel seterusnya, 45 pesakit yang didiagnosis menghidap VAP. Hanya 35/45 (78%) mempunyai keptusan kultur diagnostik yang positif. Mikroorganisma yang terbanyak daripada keputusan kultur saringan adalah *Klebsiella pneumoniae* (33/108, 30.5%), *Staphylococcus aureus* (22/108, 20.3%), *Pseudomonas aeruginosa* (11/108,10.2%), *Enterobacter* species (10/108, 9.2%), dan *Acinetobacter* species (8/108, 7.4%). Untuk sampel diagnostik, peratusan mikroorganisma adalah *Acinetobacter (16/53,*30%), *Pseudomonas aeruginosa (12/53,* 22.6%), dan *Klebsiella pneumoniae* (11/53, 20.7%). Skala persetujuan menggunakan Analisis Indeks Cohen kappa menunjukkan persetujuan yang sederhana lemah, 0.229 (mengikut jumlah kes VAP n = 45) dan persetujuan yang lemah, 0.168 apabila dikira mengikut bilangan isolat (n = 66).

Kesimpulan: Gram-negatif bakteria adalah yang terbanyak di dalam keputusan sampel saringan dan diagnostik. Ujian saringan sampel respiratori mempunyai nilai yang terhad dalam meramal mikroorganisma penyebab VAP.

ABSTRACT

Evaluation of surveillance respiratory cultures in predicting the causative agents for ventilator-associated pneumonia (VAP)

Introduction: Ventilator-associated pneumonia **(**VAP) is a significant cause of morbidity and mortality for patients who are managed in Intensive Care Unit (ICU). It is the leading cause of prolonged hospital stay, infection with multidrug-resistant organisms and increased hospital cost. Surveillance respiratory cultures are routinely done despite the absence of clinical evidence for an infection. The value of the surveillance respiratory cultures to predict the causative organism is still uncertain and debatable.

Objective: To evaluate the clinical value of respiratory culture surveillance in predicting the causative agents for VAP in ICU patients.

Methods: This was a prospective observational study which was carried out in the General ICU of Hospital Universiti Sains Malaysia, between July 2017 to December 2018. All adults' patients who were taken surveillance respiratory were included in the study. Patients were followed up till they were transferred out from the ICU. Results of respiratory culture for surveillance and diagnostic were reviewed and analysed using Cohen's kappa coefficient (κ).

Results: A total of 193 patients were included in this study. 88/193 (46%) patients had positive surveillance cultures with a total of 108 isolates. Out of 63/193 (32.6%) patients had subsequent respiratory cultures, 45/63 (71.4%) patients fulfilled the research criteria for VAP. Only 35/45 (78%) had positive diagnostic cultures. The most common microorganism isolated from surveillance respiratory cultures was *Klebsiella pneumoniae* (33/108, 30.5%). The other microorganisms were *Staphylococcus aureus* (22/108, 20.3%), *Pseudomonas aeruginosa* (11/108, 10.2%), *Enterobacter species* (10/108, 9.2%), and *Acinetobacter species* (8/108, 7.4%). The most common microorganism isolated from diagnostic cultures was *Acinetobacter* species (16/53, 30%). The other microorganisms were *Pseudomonas aeruginosa* (12/53, 22.6%), and *Klebsiella pneumoniae* (11/53, 20.7%). The level of agreement between surveillance and diagnostic culture using Cohen's kappa coefficient show only fair agreement, 0.229 (according to the number of VAP cases n=45) and slight agreement, 0.168 when calculated according to the number of isolates (n=66).

Conclusion: Gram-negative bacteria were the most common microorganism isolated in both surveillance and diagnostic culture. Surveillance respiratory cultures had limited value in predicting the causative agents of VAP. Diagnostic culture taken on suspicion or onset of VAP remained as the gold standard for the diagnosis.

1 CHAPTER 1: INTRODUCTION

1.1 LITERATURE REVIEW

Nosocomial pneumonia which includes hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) is a common nosocomial infection and it is a significant cause of morbidity and mortality in hospitalized patients. The rate of VAP in the Malaysian ICU settings previously reported being approximately 27% (1). Pneumonia occurs at a rate of between 5 to 10 cases per 1000 hospital admissions and increased by as much as 6 to 20-fold in mechanically-ventilated patients (2). The incidence of VAP had decreased steadily over the past nine years. The rate of VAP was 1.7 per 1000 ventilator days (range 0.0 – 9.8), according to the Malaysian Registry of Intensive Care (MRIC) Report for 2016 (3).

HAP and VAP accounting for 22% of all HAIs and is among the most common hospital-acquired infections (HAIs) (4). HAP was defined as an onset of pneumonia more than 48 hours after admission, while VAP refers to pneumonia that occurs 48 hours or more after endotracheal intubation (2). VAP is diagnosed with evidence of a new or progressive infiltrate on chest radiograph and at least two of the following three criteria: fever >38°C, leukocytosis or leukopenia or purulent secretions (5).

Early-onset VAP occurs within four days of intubation and mechanical ventilation, and it is generally caused by sensitive-strain microorganism, while late-onset pneumonia develops after four days and is associated with multidrug-resistant microorganisms. Patients hospitalized for two or more days before intubation frequently associated with late-onset pneumonia (6).

Mechanically ventilated patients have an increased risk for respiratory tract infection due to the presence of endotracheal tube reduces the clearance of bacteria and increases the leakage of secretion around the cuff of the tube and disable the cilliary tract activities by damaging it (7).

Tracheal or tracheobronchial colonization (TC) by bacteria may be responsible for added or super-infections and increases the risk of mortality. Tracheobronchial colonization is vital in the pathogenesis of VAP. It is possible that the microorganism present in the tracheal secretions a few days before VAP might be the causative agent of VAP (8). TC is defined as the presence of microorganisms in the samples without clinical signs of respiratory infection (9) and is common among mechanically-ventilated critically ill patients with varying incidence from 20% to 100% of mechanically ventilated patients (10). Several factors can influence TC and VAP incidences such as antibiotic therapy, the duration of mechanical ventilation, respiratory secretions sampling methods, usage of sedative and paralytic agents, supine position, and host factors (elderly, chronic lung disease, comatose state, trauma, burns, and multi-organ failure) (11).

For the diagnosis of nosocomial pneumonia, The American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) (2) suggest the use of non-invasive endotracheal aspirate (ETA) sampling rather than invasive broncho-alveolar lavage (BAL) sampling. They also recommend for each institution to produce a local antibiogram for microorganisms isolated from the respiratory tract of patients admitted in ICU since the data was different among institution. The variation could be explained by the technique of intubation, patient's clinical and individual characteristics, colonization during intubation, or lack of adequate precautions for intubation (7).

Patients with HAP, less frequently had infections with non-enteric bacteria, including *Pseudomonas aeruginosa, Acinetobacter species*, and *Stenotrophomonas maltophilia* compared with those with VAP. The causative agents for patients with VAP, as well as HAP, can be influenced by the duration of hospitalization (12). The etiologic agents vary depending on the patient's population in an ICU, hospital stay duration, underlying illness, and former antimicrobial therapy. Knowledge of local microbial flora, their sensitivity and resistance patterns are important before initiation of empiric antimicrobial therapy (13). The usefulness of routine surveillance as a tool for the identification of causative agents of nosocomial infection for the past three decades has never been proven (14). A systematic review and meta-analysis analyzed the value of lower respiratory tract surveillance cultures to predict the causative agents of VAP in adult patients. Included 14 studies published since 1994, with total of 791 VAP episodes. A sampling frequency of 2 times per week (sensitivity 0.79; specificity 0.96) is associated with higher accuracy of prediction (15).

Routine endotracheal aspirate cultures in ICUs patients may be predictive of patients who are at high risk of invasive disease and may guide the choice of appropriate empirical therapy in suspected VAP based on the predominant microorganism identified in these routine cultures (16). Michel et al. (16) proposed twice-weekly surveillance tracheal aspirate cultures in all mechanically ventilated patients to assist in the choice of antibiotic therapies when VAP is suspected. The authors reported that surveillance cultures identified the same causative agents with similar antibiotic susceptibility patterns compared to the results of broncho-alveolar lavage fluid cultures obtained when VAP was suspected in 34 of 41 cases (83%) (16).

Serial routine surveillance can distinguish a small percentage of the causative agents and are often misleading for the selection of initial antimicrobial treatment because mostly the isolated microorganism regarded as a colonizer. Many of the pathogenic microorganisms causing VAP were initially present as respiratory tracts colonizers and subsequently promote the development of VAP (17). Since there are contradictory reports on the role of routine cultures, there is a need to re-evaluate the role of colonizers in predicting the causative agents of VAP. Yagmurdur et al. (14) reported the VAP incidence in 41/59 (69%) among mechanically ventilated ICU patients admitted with acute cerebrovascular disease. The study found that the initial surveillance cultures identified the same microorganism with the same antibiotics resistance pattern in 56% of the patients (14). The diagnostic value of surveillance cultures results in predicting *Acinetobacter baumannii* VAP documented with the following values (sensitivity: 62%; specificity: 95%, positive predictive value: 87%, negative predictive value: 82% (14).

Three years continuous prospective cohort study was conducted in Hospital Universiti Sains Malaysia, Hospital Ipoh, and Hospital Terengganu found the incidence rate VAP was 26.5% (58/215) among mechanically ventilated patients in adult medical-surgical ICU. The most common microorganisms isolated from tracheal aspirates were *Klebsiella pneumoniae, Acinetobacter* species, and *Pseudomonas aeruginosa*. The majority of these microorganisms were associated with late-onset VAP (1). However, the Malaysian Registry of Intensive Care Report for 2016 reported the most common causative agents for VAP in Ministry Of Health ICU were *Acinetobacter* species (41.8%), *Pseudomonas aeruginosa* (21.4%) and *Klebsiella* species (17.2%) (3).

Seven years cross-sectional study was conducted to evaluate the causative agent of VAP among mechanically ventilated ICU patients in Kolkata, India. The author found 59.26% of them were culture positive (438 out of 739 cultures) with the most common microorganism isolated were also *Acinetobacter baumannii, Klebsiella* species, *Pseudomonas aeruginosa,* and *Proteus* species (18).

Shafi et al. (19) done a prospective study on 30 ventilated patients to find the correlation between tracheal aspirate culture and BAL culture for the diagnosis of VAP. The study reported there was a good agreement between the two cultures (kappa =0.918; 0.442 1.000), and tracheal aspirate was found to have good sensitivity (86%) but low Specificity (63%) for the diagnosis of VAP. Shin YM et al. (20) reported fair agreement between surveillance and diagnostic cultures by Kappa analysis (K= 0.22).

Brusselaers et al.'s (21) evaluate the value routine surveillance cultures to predict multi-drug resistant (MDR) microorganism in 46 mechanically ventilated burn patients with an inhalational injury. The author found that the sensitivity, specificity, positive, and negative predictive value of surveillance cultures to predict MDR etiology in subsequent VAP was 83.0%, 96.2%, 87.0%, and 95.0%, respectively (21). The discrepancies between studies and results can be explained by several factors such as patient factor, the technique of intubation, population of patients, duration of hospitalization, underlying illness, and previous antimicrobial treatment (22, 23).

Rationale of the study

Surveillance cultures are done on samples collected despite an absence of clinical features pointing to an infection at the site from which the samples were collected. Routine processing large numbers of samples will increase the laboratory cost for additional reagents and manpower to run the tests. Furthermore, the value of surveillance culture results in guiding empiric antibiotic therapy is still controversial. There are mixed data regarding the usefulness of routine surveillance respiratory culture in ICU patients. In some studies, surveillance cultures were reported as a useful predictor of drug-resistant bacterial infections, especially in VAP and bacteraemia (24-26). Other studies showed that surveillance culture results were unable to be used as a guide for the selection of appropriate initial antibiotic therapy due to their low sensitivity (17, 27).

Thus, we hope the result of this study will help us to clear up specific issues related to the usefulness of routine surveillance respiratory cultures in ICU in predicting the causative agents for nosocomial pneumonia. Endo-tracheal tubes are prone to bacterial colonization, and therefore it is crucial to interpret the culture results with the clinical presentations of the patient. Furthermore, the local data on the prevalence of the causative agents and their antibiotic susceptibility may help clinicians to select more appropriate initial antimicrobial in order to improve the outcome and to decrease the emergence of MDR microorganisms.

1.2 Objectives

1.2.1 General objective

To determine the bacteriological profile of surveillance and diagnostic culture from respiratory tract of patient from ICU and to evaluate the value of the surveillance respiratory cultures to predict the causative agents of nosocomial pneumonia.

1.2.2 Specific objectives

1. To describe the types of bacteria isolated from surveillance and diagnostic culture from respiratory tract of patient from ICU.

2. To describe antibiotic susceptibility pattern of bacteria isolated from surveillance and diagnostic culture from respiratory tract of patient from ICU.

3. To determine the value of surveillance respiratory cultures for prediction of causative agents causing nosocomial pneumonia.

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