

VENTILATOR ASSOCIATED PNEUMONIA IN A JOHANNESBURG ACADEMIC ICU



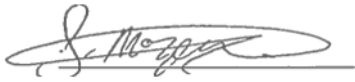
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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of
Masters of Medicine
(Internal medicine).

May 2021

Declaration

I, Sibulele Mazwi declare that this Research Report, is the product of my own unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not previously been submitted for any degree or examination at any other University.



(Signature of candidate)

__3rd__ day of __May__ 2021 in __Johannesburg__

Abstract

Introduction

Ventilator associated pneumonia (VAP), defined as a parenchymal lung infection occurring 48 hours or more after onset of mechanical ventilation, and has been recognised for at least the last two decades as one of the common infections in the intensive care unit (ICU). It has an estimated incidence of 10 to 41.5 per 1000 ventilator days in developing countries and carries a high mortality estimated at 24 to 50%. VAP is an entity that is poorly researched in South Africa, specifically in the adult population, with little known about local prevalence and outcomes.

Aim

To describe Ventilator associated Pneumonia (VAP) in a tertiary public hospital in Johannesburg, and assess the microbiological pathogens associated with VAP (both early and late) and outline the outcome of these patients.

Methods

A retrospective record review of patients admitted to Helen Joseph Hospital (HJH) ICU between the period of March 2013 and December 2015. All patients with the diagnosis of VAP were identified from the ICU data base and their records extracted from the hospital records and reviewed. Data was then consolidated from patient records as well as from NHLS digital record system.

Results

The percentage of patients admitted to ICU who developed VAP was 2.9% (95% CI 1.8- 4.2%) 24 out of 842 ventilated patients, with incidence rate of 16.4 per 1000 ventilator days during the period 2013- 2015. Regarding outcome of VAP in this cohort, 29.2% died while 70.8% were discharged from ICU. Post ICU outcomes of these patients are beyond the scope of this research. Late-onset VAP (after 5 or more days of ventilation), with incidence of 45.8% was associated with much higher mortality of 54.6%, compared to early-onset VAP which had a incidence of 54.2%, and a mortality of 7.7%. Commonly isolated organisms included *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Proteus mirabilis*. The trend toward increased risk of multi-drug resistant organisms remained with late onset VAP - adjusted RR [aRR] 2.26 (95% CI 0.92- 5.57), p-value = 0.077, and airway access through tracheostomy (relative risk [RR] 1.68 (95% CI 0.78- 3.57).

Conclusion

This study shows a low moderate incidence of VAP of 16.4 events per 1000 ventilator days, with the lowest being 10 events per 1000 ventilator days. A tracheostomy and late onset VAP are associated with infection by drug resistant organisms. The study reveals a mortality of 29.2% in this setting, with a seven-fold increase in mortality with late onset VAP.

Acknowledgements

I would like to thank my family, especially my wife Thumeka Mpata, for the continued support and patience throughout this journey.

I also would like to extend my special thanks to Dr Murimisi Mukansi and Dr SA van Blydenstein, my supervisors, for the guidance they provided in the production of this work.

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Nomenclature

ARDS	Acute respiratory distress syndrome
ATS	American thoracic society
CDC	Centre for disease control
CF	Cystic fibrosis
COPD	Chronic obstructive pulmonary disease
CPIS	Clinical pulmonary infection score
CRE	Cabapenem resistant <i>enterobacteritiae</i>
DVT	Deep vein thrombosis
ETT	Endotracheal tube
HAI	Hospital acquired infections.
HELICS	Hospitals in Europe Link for Infection Control through Surveillance
HIV	Human immunodeficiency virus
HJH	Helen Joseph Hospital
HPCSA	Health professionals council of South Africa
HREC	Human research ethics committee
ICU	Intensive care unit
IDSA	Infectious disease society of America
MDR	Multi-drug resistance
MDRO	Multi-drug resistant organisms
MRSA	Methicillin resistant <i>Staphylococcus aureus</i>
NICE	National institute for health and care excellence
NHLS	National health laboratory services
PEEP	Positive end expiratory pressure
TB	Tuberculosis
USA	United States of America
VAP	Ventilator associated pneumonia.

VAT	Ventilator associated tracheobronchitis.
VRE	Vancomycin resistant <i>enterococcus</i>
WCC	White cell count
WITS	University of the Witwatersrand

Chapter 1

1. Introduction and literature review

1.1 Background

Ventilator associated pneumonia (VAP), defined as a parenchymal lung infection occurring 48 hours or more after onset of mechanical ventilation, has been recognised for at least the last two decades as one of the concerning infections in the intensive care unit (ICU). In clinical settings it is usually divided into early and late, that being within four days post intubation (early)- and after five days or more (late). This distinction is important as it relates to the microbiology of the pathogens and therefore treatment strategies. It has an estimated incidence of 10 to 41.5 per 1000 ventilator days in developing countries and carries a high all-cause mortality estimated at 24 to 50%(1,2). The crude VAP related mortality is debatable with reported incidences of 13 to 39.8%(1,3). VAP is an entity that is poorly researched in South Africa, specifically in the adult population, with little known about local prevalence and outcomes(4).

1.2 Literature review

1.2.1 Introduction

The entity of VAP has been recognised for at least the last two decades(2). For years it has been known to be one of the common infections in the ICU with estimated incidence between 8 and 28% (10 to 41,5 per 1000 ventilator days in developing countries)(2,5,6). VAP carries high mortality rates ranging from 24 to 50%, and can be as high as 76% in developing countries(1,3).

Throughout the world, however, it has been difficult to delineate the true prevalence of VAP due to multiple challenges in the diagnosis of this condition, central to which is the lack of a gold standard for diagnosis and therefore no standardised diagnostic criteria(6).

Ventilator associated pneumonia is currently defined as a parenchymal lung infection occurring forty-eight hours or more after onset of mechanical ventilation with intubation by either endotracheal or tracheostomy tube, which was not there at time of intubation and initiation of ventilation(1,6,7). In clinical settings it is usually divided into early and late, that being within four days (early) and after five day or more (late)(6,8). This distinction is important as it relates to the microbiology of the pathogens and therefore treatment strategies. Late VAP is more likely due to multi-drug resistant organisms than early VAP(1).

As previously stated, there is no gold standard diagnostic criteria, the Johansson Criteria is the most widely accepted. It states that a new or progressive infiltrate and two of three clinical features (namely, leucocytosis, purulent secretions, and pyrexia of more than 38°C) constitute a diagnosis of VAP. The clinical pulmonology infection score (CPIS), the United States of America Centre for Disease Control (CDC) criteria and the Hospitals in Europe Link for Infection Control through Surveillance (HELICS) criteria have been used either in clinical or research or public health environments(1,2,9).

In addition to the above parameters, there are other parameters that help with formulating a more extensive criterion to minimise the number of missed cases. Below are all characteristics considered in calculating the CPIS and formulating a diagnosis of VAP(10,11).

1.2.2 Clinical features, radiology, and microbiological diagnosis

These include signs and symptoms of systemic inflammation (Fever > 38°C, white cell count (WCC) >12 x10⁹cells/L or <4x10⁹cells/L and confusion for the elderly) and respiratory system specific signs and symptoms (desaturation, PaO₂/FiO₂ <241, cough, purulent sputum, increased secretions, shortness of breath and rales or bronchial breathing)(1,2,7,9–11).

The features on radiology are two or more plain chest X-rays with new, progressive, or persistent infiltrate or consolidation with or without pleural effusion(7,10,11).

Microbiologically, a positive culture in blood or pleural effusion, quantitative culture > 10⁵ cfu/mL on bronchial lavage, or histo-pathological evidence of infection is required for diagnosis(1,10).

Of note, the features of VAP overlap with other common conditions in the ICU environment such as acute respiratory distress syndrome (ARDS), atelectasis and other ICU infections. In fact, one of the challenges with VAP diagnosis is ventilator associated tracheobronchitis (VAT), which holds a similar clinical presentation except that VAT has no evidence of desaturation or X-ray features of pneumonia. VAT actually has the potential to develop into VAP in 30% of cases(6).

Risk factors for VAP are endotracheal intubation and prolonged mechanical ventilation. Advanced age, immunosuppression and malnutrition are some of the factors that hamper host response. Aspiration during intubation or past an insufficiently inflated cuff, pre-existing sinusitis/lung disease and chronic lung disease allow for pathogen entrance and proliferation. Obesity is also a known risk factor, probably related to increased risk of aspiration during intubation and difficulty in upper body elevation during ventilation(6,7,12).

1.2.3 Pathogenesis

The pathogenesis of pneumonia stems from invasion of the lower respiratory tract and lung parenchyma by microorganisms(1,6).

The two most important causes of VAP are:

- a. Biofilm establishment within the tube lumen (endotracheal tube (ETT)/tracheostomy)
- b. Micro-aspiration of secretions particularly subglottic and above the tube cuff.

The presence of the tube in the trachea alters the natural defence mechanisms, thus allowing micro-aspiration and for the aspirated particles to pass into the lower respiratory tract. Supine positioning of the patient further compounds the problem. Patients on nasogastric tube feeds have a higher chance of gastric aspiration. The tube biofilm is pushed further down the respiratory tract by the ventilator cycles and serve as a nidus for infection. Host factors, particularly immunosuppression (which could be multifactorial) with critical illness playing a major role(9).

1.2.4 Aetiological agents

The common microorganisms isolated in VAP are Gram-negative bacilli accounting for 60% of cases in studies of the developed world and 41-92% reported in the developing world(3,5,9,13). Of these *Pseudomonas aeruginosa* (63.7% of Gram-negatives) is the leading organism followed by *Acinetobacter* species and then by *Proteius mirabillis*, *Escherichia coli*, *Klebsiella* species and *Haemophilus influenza*(13).

Gram-positive cocci account for a substantial percentage of cases with documented *Staphylococcus aureus* accounting for 20% of cases in the developed world. Gram-positive cocci in total make up 6-58% of cases in developing countries(2,5,13).

A small percentage is caused by fungi (0.9% reported in the United States of America (USA) and up to 7% in developing countries) the majority of which is due to *Candida* species(1,2,5). There are certain factors associated with specific bacterial population such as patient comorbidities e.g., chronic obstructive pulmonary disease (COPD) and Cystic fibrosis (CF). Late onset VAP is known to most commonly be associated with resistant organisms (i.e., carbapenem resistant enterobacteriaceae (CRE), vancomycin resistant *enterococcus* (VRE), methicillin resistant *Staphylococcus aureus* (MRSA), *Pseudomonas* and *Acinetobacter* species). prior exposure to anti biotics and an increasing colonization of units by MDR organisms being major contributors (8,12–15).

1.2.5 Risk factors associated with VAP and multi-drug resistance (MDR)

There are various risk factors for VAP. Patients' characteristics (e.g., advanced age > 65 years, male sex and smoking), increased mechanical ventilation time and prolonged mechanical ventilation, disorders of consciousness and head trauma, burns, comorbidities (coronary heart disease, diabetes, pre-existing pulmonary disease/COPD, AIDS and multiple-organ system failure), prior antibiotic therapy, invasive operations, and gene polymorphisms are the internationally recognized independent factors of VAP at present(16,17).

Non-modifiable treatment-related risk factors include the necessity of neurosurgery, monitoring of intracranial pressure, reintubation, and transportation out of ICU(17).

The well-established risk factors for MDR organisms are: prior intravenous antibiotic use within ninety days; septic shock as defined by the third international consensus definitions for sepsis and septic shock (sepsis-3) at time of VAP; ARDS preceding VAP (high index of suspicion required for one to make a diagnosis in this case); five or more days of hospitalisation prior to VAP; and acute dialysis prior to VAP(2,3,12,18).

1.2.6 Prevention

The prevention of VAP is based on trying to mitigate the modifiable risk factors and intervene on the main pathogenic factors mentioned above. It is for this reason that many organisations, including the National Institute for Health and Care Excellence (NICE), have developed care bundles for VAP prevention. The 2008 NICE bundle document had four care interventions namely, daily sedation holds, bed head elevation, gastric ulcer prophylaxis and oral care. The version of care bundles mostly employed was updated in 2010 and it includes oral hygiene with adequate anti-septic, subglottic aspiration and ETT cuff monitoring(1,7,19,20).

Also to note as part of or supplementary to the bundle of care are appropriate humidification of inspired air, deep vein thrombosis (DVT) prophylaxis, suctioning of secretions and appropriate tubing management (such as avoiding un-necessary circuit tubing changes)(11,20). These bundles have shown some effectiveness in VAP prevention. This requires good nursing education and studies have shown that nursing care education is key to VAP prevention(20).

Other areas of prevention that show potential in further decreasing VAP rates have been studied or are being studied. These include:

a. Tracheal tube modification

Cuff pressure control: firstly, pressures between 20-30 cmH₂O are desirable, secondly, cuff design (polyurethane cuffs seem to prevent aspiration better than polyvinyl chloride cuffs), thirdly, cuffs that allow for subglottic secretion drainage (thus decreasing available content for micro aspiration), and lastly, tracheal tube coating (silver chlorhexidine or titanium coated tubes seem to prevent VAP)(9).

b. Inhaled antibiotics

Colistin and gentamycin have been the most studied, and although colistin does decrease VAP rates, it is associated with an increase in antibiotic resistance. Gentamycin on the other hand does decrease biofilm of the tube but does not necessarily decrease VAP. For these reasons use of aerosolised antibiotics is not recommended for prevention purposes currently(9).

1.2.7 Management

The 2016 clinical practice guidelines by the Infectious Disease society of America (IDSA) and the American Thoracic society (ATS) guide management of VAP currently. These guidelines recommend that each individual ICU should develop its own antibiogram to refer to, on the basis of local anti-microbial resistance patterns(1).

Antimicrobial treatment is divided into empiric and definitive. Definitive treatment is based on culture results as well as sensitivity and therefore can only be executed when such results are obtained. Due to the high mortality rate from VAP, empirical treatment is necessary while culture results are still pending(1,21). The recommendation is that empiric combination therapy should cover Gram negative bacilli and MRSA, and culture directed therapy be initiated as soon as culture results are available. The recommended duration of therapy is seven days(1,11).

There is paucity of data pertaining to prevalence of VAP in South Africa, including that relating to the most common culprit organisms for this disease, thus hampering guideline development, especially for the adult population.(4)

1.3 Study Aims and Objectives

To describe VAP in a tertiary public hospital in Johannesburg, to describe the epidemiology, microorganism and outcome of patients presenting with VAP in a tertiary hospital presenting

with early and late onset VAP. The study also aims to examine the commonly isolated organisms and their distribution amongst VAP patients and compare the out-comes to those demonstrated in other countries, both developing and developed countries.

The objectives are primary and secondary.

Primary

1. To identify the proportion of patients intubated at the Helen Joseph Hospital (HJH) ICU who go on to develop VAP.
2. To identify the predisposing factors described in literature for development of VAP and identify those that occur most frequently in this cohort.
3. To describe the microbiological pathogens associated with early and late VAP.
4. To describe the outcome of patients diagnosed with early and late VAP in HJH ICU.

Secondary

1. Describe the proportion and time of early and late onset VAP.
2. Determine which of the predisposing factors are associated with multi drug resistant organisms.

Chapter 2

2 Methodology

2.1 Study site

A retrospective record review of patients admitted to Helen Joseph hospital ICU between the period of March 2013 and December 2015, a period of 1460 days. Helen Joseph Hospital is a tertiary care centre attached to the University of the Witwatersrand (WITS).

All relevant microbiology results were extracted from the in Hospital National Health Laboratory Service (NHLS) laboratory where they are all processed.

2.2 Study population

All patients admitted to this ICU are recorded on a patient register with their corresponding diagnosis both provisional and definitive. All patients with the diagnosis of ventilator associated pneumonia were identified and their records were retrieved from the hospital records. These were further filtered to those that fit the diagnosis as defined below. Data from these files was then collected using the Data sheet in Annexure A.

2.3 Study definitions

Ventilator associated pneumonia (VAP)- was defined as pneumonia occurring in a mechanically ventilated patient which was not there at time of intubation and initiation of ventilation and occurring 48 hours or more after onset of ventilation. It is characterised by a new, persistent or progressive infiltrate on chest radiography, change in temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, production of purulent endotracheal secretions, requirement of a change in PEEP or FiO_2 to maintain saturation of $>90\%$ (1,6,7).

Multi-drug resistance is defined as resistance to at least one agent in three or more antimicrobial classes, as per NHLS microbiologic testing.

Inclusion criteria

- Age > 18 years old.
- With characteristics meeting our definition of VAP.

Exclusion criteria

1. Patients who developed pneumonia within 48 hours of admission.
2. Patients admitted with a diagnosis of pneumonia.
3. Patients with ARDS.

4. Mechanically ventilated patients who died within 48 hours from admission.

2.4 Data collection

Data collected included:

Demographics, clinical data, measures taken to prevent hospital acquired infections (HAI), investigations performed (blood, radiology, endotracheal specimen), disease severity at the onset of VAP and the management approach employed. (Annexure 1).

To identify the organisms that were the causative pathogens in our VAP population, a track care lab search was carried out with the patient hospital numbers, as well as with the names and surnames to maximise search results.

2.5 Data management and analysis

Data captured in Excel was exported into Stata 14.2 for analysis. Following data cleaning and recoding variables, descriptive statistics were used to describe individuals admitted into ICU and developed VAP. Median and interquartile ranges were used for continuous variables which frequencies and percentages were used for categorical data. Analysis methods for the primary and secondary objectives are described below.

1. To identify the proportion of patients admitted to the Helen Joseph hospital intensive care unit who go on to develop ventilator-associated pneumonia- this was determined as number of patients who developed VAP / total number of ICU admissions and presented as a percentage as well as events per 1000 ventilator days with a 95% confidence interval. The number who developed VAP was obtained from the database of VAP patients while aggregated ICU data was used to obtain the number admitted into ICU.
2. To determine the predisposing factors for development of VAP and identify those that occur most frequently- because individual level data was collected for VAP patients only, the prevalence of specified risk factors was determined and presented as frequencies and percentages.
3. To assess the microbiological pathogens associated with VAP both early and late- the proportion of VAP patients who different organisms detected on endotracheal aspirate and blood specimens were determined as frequencies and proportions and presented by early or late VAP status.
4. Outline the outcome of patients diagnosed with ventilator associated pneumonia in Helen Joseph hospital ICU- this was determined as proportions for all patients with VAP and by early or late VAP status.
5. Estimate the time it takes from admission (intubation and ventilation) to development of ventilator associated pneumonia- this was determined as the number of days between admission and VAP diagnosis and presented as median with an interquartile range.

6. Determine which of the predisposing factors are associated with multi drug resistant organisms- univariable and multivariable Poisson regression with robust error variance was used to determine factors associated with detection of MDR organisms from tracheal aspirate or blood specimens. Variables which had a p-value <0.2 in univariable analysis were included in the multivariable analysis. The estimate of the relative risks associated with the different factors were reported with a 95% confidence interval (CI).

2.6 Ethics

The research proposal was submitted to the Human Research Ethics Committee (HREC) and forwarded to the post graduate committee of the Wits University for approval (M190124). Permission to perform the study was obtained from HJH head of ICU, and HJH research committee through the hospital CEO and clinical manager. Approval for the research was granted prior to any data collection.

Data was collected from patient records as well as from NHLS digital record system. Patient information was kept confidential, and no patient identity will reflect on reported data. No patient consent was required as above was observed and all information was obtained from already existing data (retrospective study).

The HPCSA general ethical guidelines for health researchers were adhered to.

2.7 Cost

The expected costs are related to stationery and printing and were paid for by me. These are estimated at; printing R2400.00 and stationary R1150.00.

2.8 Study limitations

The data for this study was collected from a pre-existing data base as this is a retrospective study and elements of the data we required may have been missing as they were subject to having vigilant, usually junior doctors updating it. The study was initially intended to cover a period as far back as 2011 July, but due to flooding of the Helen Joseph archive area, as well as change in the laboratory system from DISA to lab trackcare, data for patients admitted during the time prior to 2012 could not be accessed. The absence of a control arm for the assessment of risk factor prevalence meant that only the prominent characteristics in this cohort known to be risk factors could be highlighted.

Chapter 3

3 Results

3.1 To identify the proportion of patients admitted to the Helen Joseph Hospital intensive care unit who go on to develop ventilator associated pneumonia.

The proportion of patients admitted to ICU who developed VAP was 2.9% (95% CI 1.8-4.2%).

The 24 VAP cases occurred over 1460 days of admission. The VAP incidence rate = 16.4 cases/ 1000days of admission assuming that there was at least one ventilated patient in ICU for every day during this period.

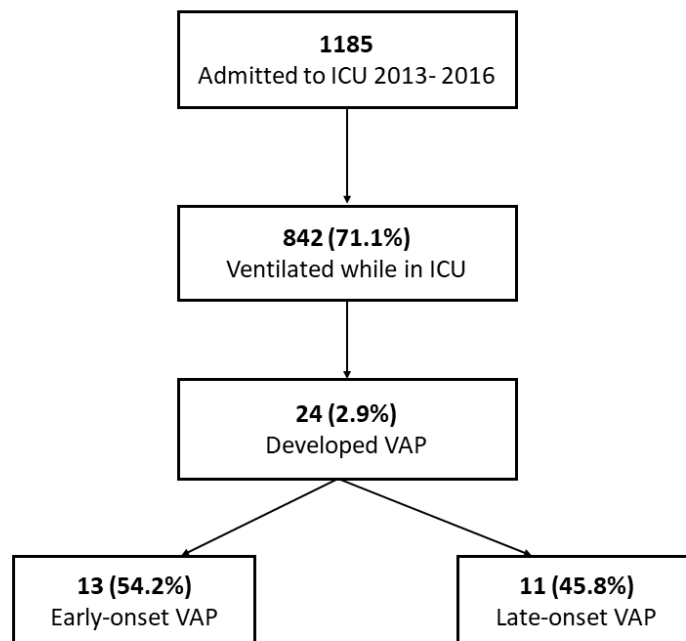


Figure 3.1: Summary of patient flow

3.2 Determine the predisposing factors for development of VAP and identify those that occur most frequently.

As there was no data collected on admitted patients who did not develop VAP, a risk factor analysis could not be done. Table 1 below presents the demographic and clinical characteristics who developed VAP.

Table 3.1: Demographic and clinical characteristics of patients who developed VAP at admission (N=24)

Characteristic	n (%)
Age (median, IQR)	40 (29- 62)*
Males	18 (75)
One or more comorbidities	7 (29.2)
Admission source	
Emergency/Casualty	12 (50)
Medical inpatients	8 (33.3)
Surgical inpatients	2 (8.3)
Other	2 (8.3)
Diagnoses at ICU admission	
Medical	11 (45.8)
Trauma	9 (37.5)
Surgical	3 (12.5)
Missing	1 (4.2)
Airway access at admission	
Endotracheal tube	83.3
Tracheostomy	16.7
Indication for ventilation	
Respiratory failure	8 (33.3)
Airway protection	13 (54.2)
Anaesthesia	3 (12.5)
Head of bed elevated	24 (100)
Adequate sedation provided	23 (95.8)
Oral care provided	24 (100)
Antacid provided	24 (100)
HIV status	

Positive	7 (29.2)
Negative	9 (37.5)
Unknown	8 (33.3)
White blood cell count ($\times 10^6$ cells/L), median (IQR)	12.8 (8.8 -17.8) *
Length of stay in ICU in days (median, IQR)	12 (9- 15)*
Time on antibiotics (days)	7 (7-8)

*median and interquartile range (IQR)

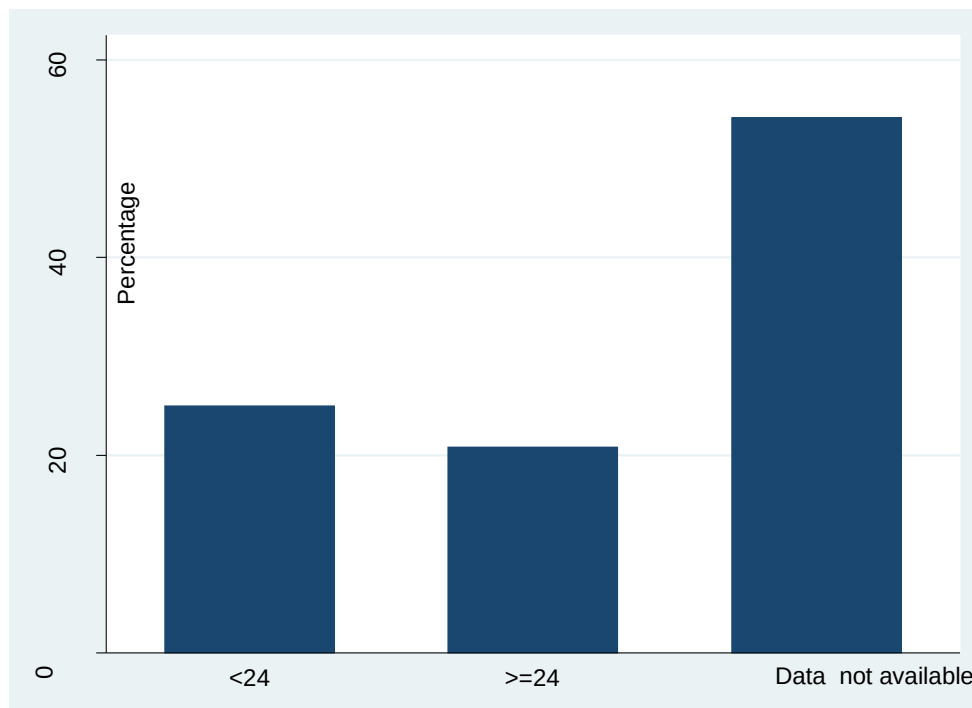


Figure 3.2: APACHE II scores among patients admitted with VAP (N=24)

Figure 2 presents the APACHE II scores at admission. APACHE II scores were available for 11/24 (45.6%) of the patients. Of the 11 for which scores were available, 5(45.5%) had score ≥ 24 while 6 (54.5%) had scores < 24 .

3.3 To assess the microbiological pathogens associated with VAP both early and late

Of 24 patients who developed VAP, 17 (70.8%) had an organism isolated from ETA specimens. The distribution of the organisms isolated are shown in Figure 3 below.

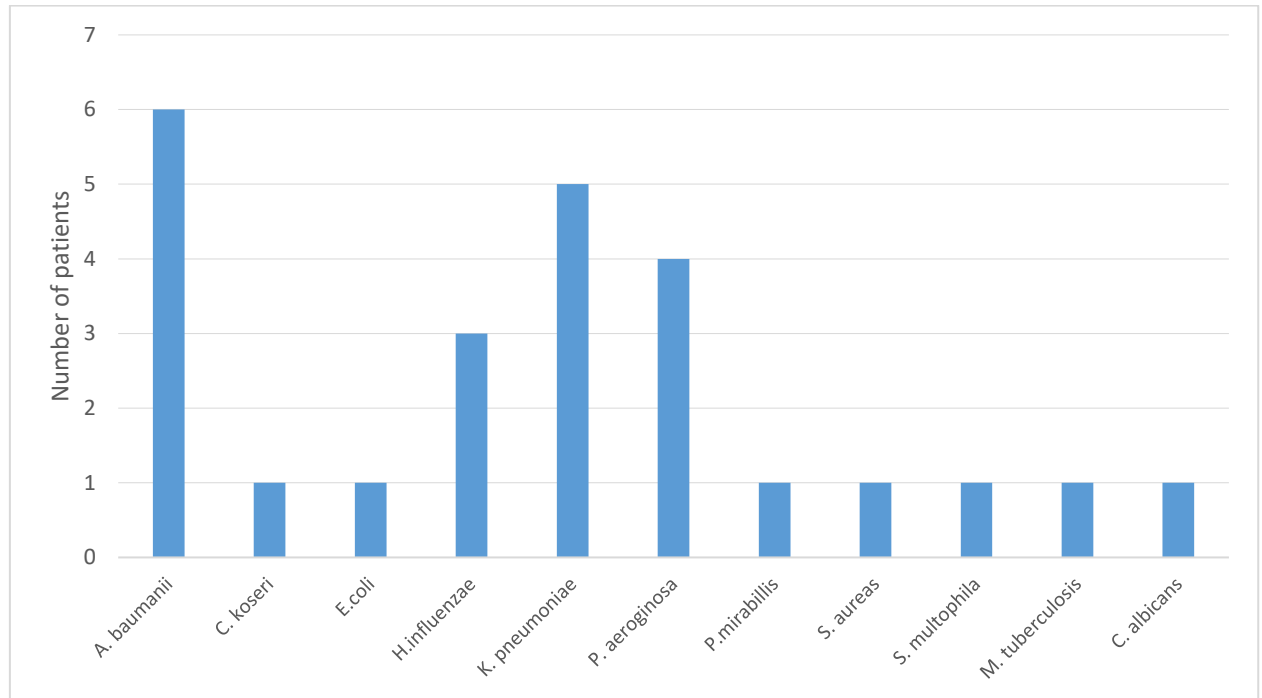


Figure 3.3: Distribution of pathogens in endotracheal aspirates of patients who developed VAP (N=17)

Of 13 patients who had early-onset VAP, 7 (53.8%) had an organism isolated from ETA specimens while of 11 patients with late-onset VAP, 10 (90.9%) had an organism identified. The distribution of the organisms isolated by onset of VAP are shown in Figure 4.

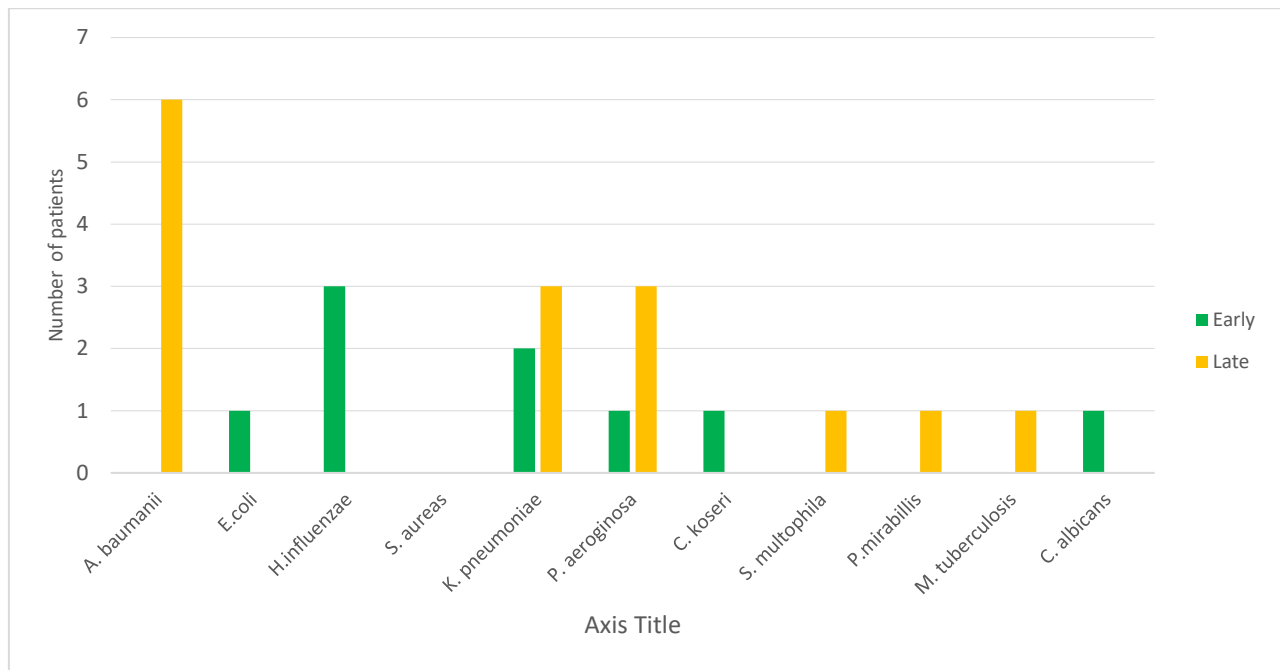


Figure 3.4: Distribution of pathogens in endotracheal aspirates of patients who developed VAP by onset of VAP (N=17)

Of the 24 patients who developed VAP, 11 (45.8%) had organism isolated on blood culture. Of these 11, 4 had early-onset VAP while 7 had late-onset VAP.

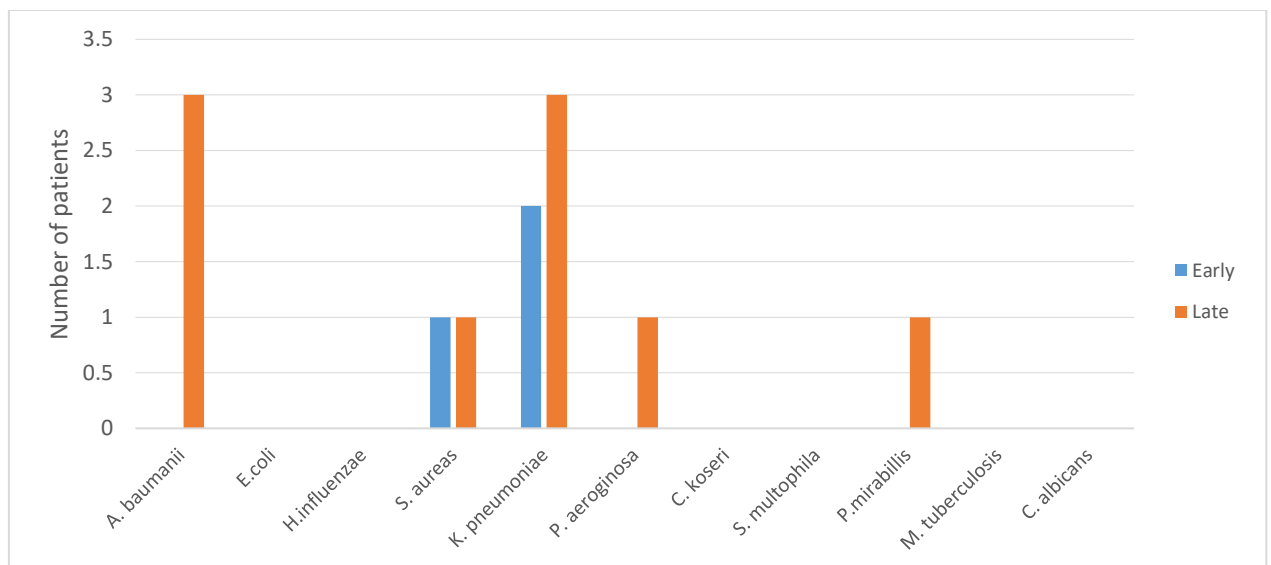


Figure 3.5: Distribution of pathogens in blood cultures of patients with VAP by onset of VAP (N=21)

Figure 6 below shows the distribution of the multi drug resistant organisms we had isolated on our samples, of which the majority were Gram negative bacilli.

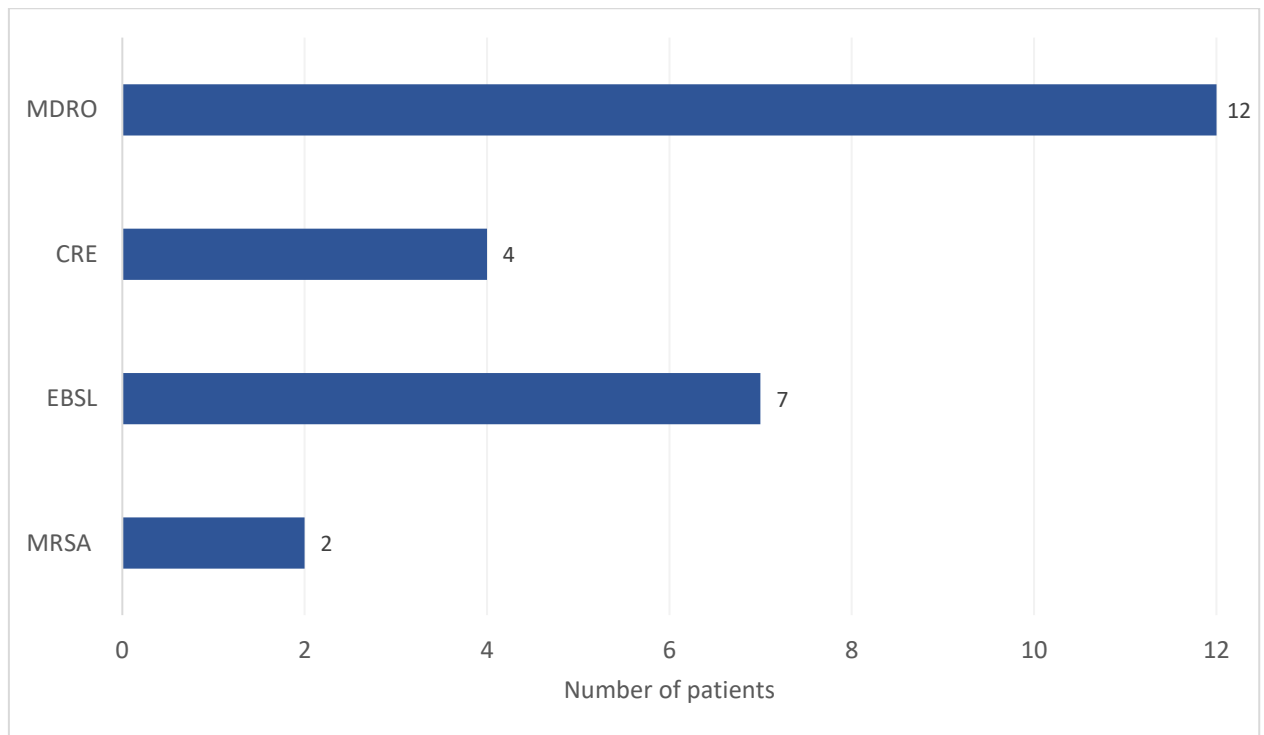


Figure 3.6: Number of VAP patients by MDRO type

3.4 Outline the outcome of patients diagnosed with ventilator associated pneumonia in Helen Joseph Hospital ICU

Of the 24 patient who had VAP, 7 (29.2%) died, while the remaining 17 (70.8%) were discharged from ICU. Late-onset VAP was associated with much higher mortality 6/11 (54.6%), compared to early-onset VAP 1/13 (7.7%); X^2 p-value =0.018

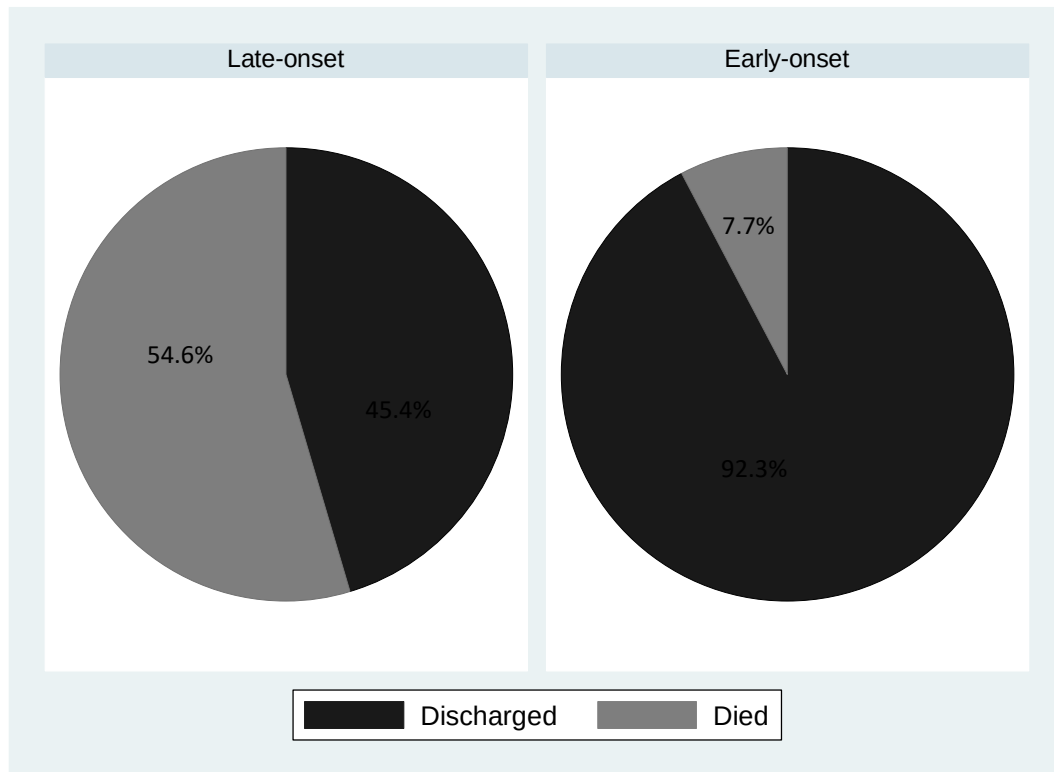


Figure 3.7: Outcomes of VAP by onset

3.5 Estimate the time it takes from admission (intubation and ventilation) to development of ventilator associated pneumonia

The median time from intubation and ventilation to VAP diagnosis was 3 days (IQR 2-5.5days). The median time to diagnosis was longer among those with late-onset VAP compared to those with early-onset VAP- 6 days (5- 8 days) for late-onset compared to 2 days for early-onset; p-value for the Wilcoxon rank sum test <0.001

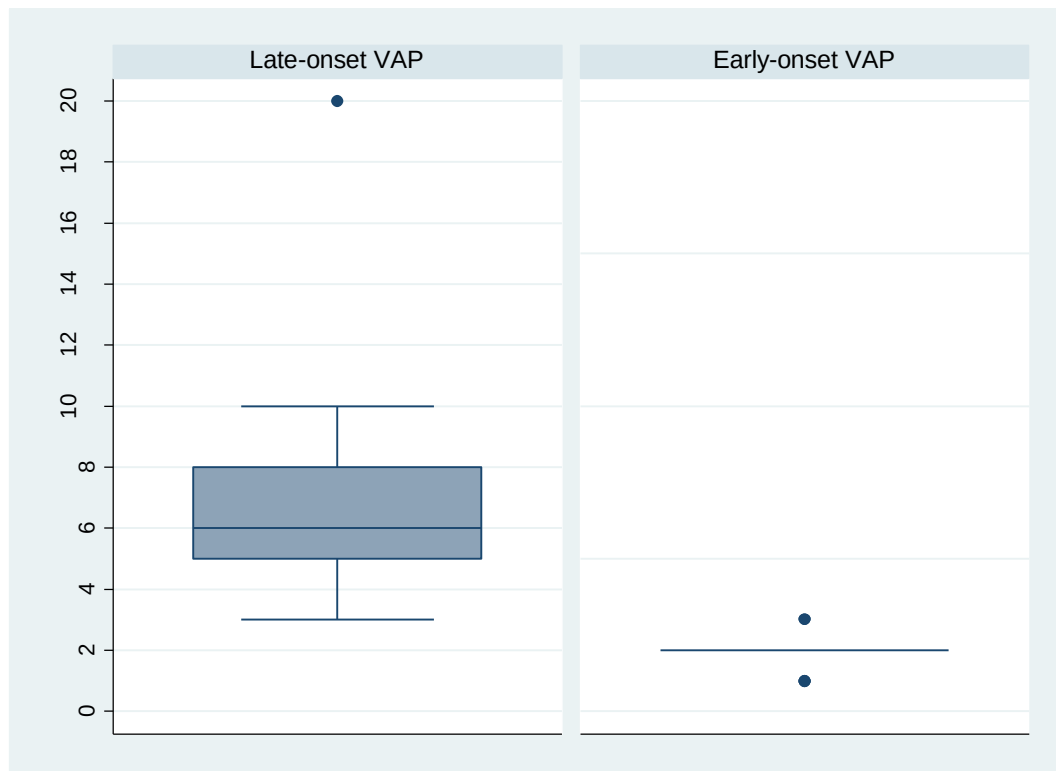


Figure 3.8: Time from intubation to VAP diagnosis by onset

3.6 Determine which of the predisposing factors are associated with multi drug resistant organisms.

Overall, 12/20 (60%) of patients who had organisms cultured on either tracheal aspirate or blood had a MDRO identified. Table 2 below show the factors associated with having an MDRO identified, comparing patients with MDRO to those with no growth or were drug sensitive organisms.

Table 3.2: Factors associated with identification of an MDRO (N=24)

Variable	n/N (%) with MDRO	Univariable RR(95% CI)	p- value	Multivariable aRR (95% CI)	p- value
Age <=50 years					
No	4/10	1.00			
Yes	(40.0) 8/14 (57.1)	1.42 (0.59-3.52)	0.429		
Gender					
Female	3/6 (50.0)	1.00			
Male	9/18 (50.0)	1.00 (0.40-2.57)	0.999		
Has comorbidity					
No	9/17(52.9)	1.00			
Yes	3/7 (42.9)	0.81 (0.31-2.17)	0.668		
HIV positive					
No	6/9(66.6)	0.93			
Yes	5/7 (71.4)	1.07 (0.82-3.68)	0.617		
Unknown	3/8(37.5)				
Admission period					
2015/16	5/17	1.00		1.00	
2013/14	(35.7) 7/10 (70.0)	1.96 (0.86-4.49)	0.112	1.89 (0.81- 4.42)	0.140
Airway access					
ETT		1.00		1.00	

Tracheostomy	9/20 (45.0) 3/4(75.0)	1.68 (0.78-3.57)	0.188	0.75 (0.36-1.58)	0.456
Ventilation					
Indication	5/11	1.00			
Other	(45.5)	1.18 (0.52-2.74)	0.692		
Airway protection	7/13 (53.9)				
Diagnosis at ICU					
diagnosis	7/13	1.00			
Other	(53.9)	0.84 (0.37-1.95)	0.686		
Medical	5/11 (45.5)				
Onset of VAP					
Early	4/13	1.00		1.00	
Late	(30.8)	2.36 (0.95-5.88)	0.064	2.26 (0.92-5.57)	0.077
	8/11 (72.7)				

In univariable analyses, there was a trend towards increased risk of MDRO with airway access through tracheostomy (relative risk [RR] 1.68 (95% CI 0.78- 3.57), being admitted in ICU during the period 2013/2014 – RR 1.96 (95% CI 0.86- 4.49) and with late-onset VAP – RR 2.36 (95% 0.95- 5.88). In the adjusted analyses, the trend toward increased risk of MDRO remained with late onset VAP - adjusted RR [aRR] 2.26 (95% CI 0.92- 5.57), p-value = 0.077, and with admission during the period 2013- 2014 - aRR 1.89 (95% 0.81- 4.42) p=0.140.

3.7 Summary of results

The study described patients admitted to the Helen Joseph hospital ICU over a 1460-day period. Most patients admitted to this ICU are ventilated (71%) and are admitted from both medical and surgical wards. Of those ventilated, 2.9% had a diagnosis of VAP at the end of ICU stay, which equates to 16.4 events per 1000 days.

The prevalence of both early and late VAP seems to be even, at 54.2% and 45.8% respectively. In terms of isolated pathogens however, Gram-negative bacilli were isolated more frequently in the late VAP group. Over two thirds (70%) of the VAP patients had an

organism isolated on respiratory specimens (tracheal aspirates) while 45.8% were blood culture positive.

The median time from intubation and ventilation to VAP diagnosis was 3 days (IQR 2-5.5days). An analysis of risk factors revealed that advanced age is not a significant risk factor in our cohort, while the male gender, prolonged ventilation time, and presence of comorbidities including being HIV positive are common risk factors. We could not, however, identify risk factors predisposing to VAP in our patient group as this would require the presence of a control arm. We did, however, identify factors associated with multi drug resistant organisms. These are: airway access through tracheostomy (relative risk [RR] 1.68 (95% CI 0.78- 3.57); being admitted in ICU during the period 2013/2014 – RR 1.96 (95% CI 0.86- 4.49); and with late-onset VAP – RR 2.36 (95% 0.95- 5.88).

Of the patients who had VAP, 29.2% died, while the remainder were discharged from ICU. Late-onset VAP was associated with much higher mortality (54.6%) compared to early-onset VAP (7.7%) χ^2 p-value =0.018.

Chapter 4

4 Discussion

4.1 Incidence

A retrospective data collection and analysis was carried out on patients diagnosed with VAP over a period of 1460 days for the period 2013 to 2016. Patients who were diagnosed with VAP at the end of their ICU stay as entered on the HJH ICU patient data base were identified. During this period, there were 1185 admitted patients (0.8 admissions per day) and 71.1% of these were ventilated patients (0.57 vent admissions per day). Since this is an ICU that has less than 14 beds, it would generally be classified as a small ICU unit, and the admission numbers are comparable to those seen in America (mean 2.1 $\pm$ 1.3 admissions per day)(22). The comparison of these findings to those of other low income countries has proven difficult due to low ICU capacity of such countries as well as the poor availability of data from these countries(23).

The overall average length of stay in this unit during this period was 15 days for the VAP patients which is almost similar to the 13-day average observed in other parts of the world(24). The ICU in the study has a rapid turnover, due to high demand, with occupancy at any given time at or around 90%.

The absolute percentage of patients who were diagnosed with VAP in this unit is 2.9% of all ventilated patients as demonstrated in Figure 3.1. The incidence however is 16.4 events per 1000 ventilator days. This assumes that there was at least 1 ventilated patient per day in the unit. In comparison to the rest of the world, this falls within the average incidence of VAP which varies widely from 10 to 41.5 episodes per 1000 ventilator days(5).

The incidence of VAP in this unit falls on the low end of average for ICUs in developing countries, however, some areas of the world have reported even lower numbers in ICUs of a heterogeneous nature like the one studied(25,26) . This could be attributed to a few possible factors. As noted on Table 3.1, there is a strict adherence in the unit to care bundles to reduce complications in ICU such as VAP. The diagnosis of VAP at the time was mostly defined based on the CPIS index, which has a high inter-observer variability in its calculation therefore limiting its diagnostic impact(4,9,10). Therefore, subtle cases may have been missed. There exists vast differential diagnosis to be considered in the process of diagnosing VAP a limitation that has been observed in units elsewhere(10).

In trauma patients, especially head trauma in whom a comatose state is a major risk factor for early VAP, one had to consider aspiration syndromes such as Mendelson syndrome as

probable diagnoses, prior to coming to a diagnoses of VAP, which then further reduces number of people diagnosed as early VAP(27). There was no follow up of post ICU outcomes for these patients, therefore, those with a diagnoses of Hospital acquired pneumonia post ICU and treated in the ward, falling into the category of nosocomial pneumonia who may otherwise meet criteria for VAP were not included in the study (28). The possibility of underdiagnosing VAP is also a consideration especially since post-mortem studies evaluating the effectiveness of clinical criteria for VAP diagnosis show that these criteria have a 69% sensitivity(10).

The major question then is, are these findings surprising or satisfactory. The answer to that question is both, surprising because South Africa is a developing country and as such one would have expected a higher prevalence, as we have seen, low to middle income countries report higher incidences than high income counterparts(5,29). However, taking into consideration the fact that we studied an urban ICU in an academic environment, this might be a mitigating factor and therefore have the studied ICU perform at standards as close to the developed world as can be expected. We find these findings satisfactory because, ultimately the aim is to prevent VAP.

The measures available for preventing this disease are correctly following good contact precaution practise and basic care bundles. Studies to determine whether care bundles do indeed prevent VAP are equivocal for the most part(19). The biggest role player in their success is the dedication of the nursing teams, as these are the professionals who are ensuring adherence on a continuous basis(20,30). As demonstrated in Table 1, at least 95.8% of the time, the minimum requirement of care bundles, head elevation, adequate sedation, antacids, and oral care, as written on the 2008 NICE bundle document, were adhered to. Inhaled antibiotics are not used in the centre studied, as such, there can be no comment on the effectiveness of this strategy in both prevention and management of VAP.

4.2 Predisposing factors

There are various risk factors for VAP. Patients' characteristics (e.g., advanced age > 65 years, male gender, and smoking), increased mechanical ventilation time and prolonged mechanical ventilation, disorders of consciousness and head trauma, burns, comorbidities (coronary heart disease, diabetes, pre-existing pulmonary disease/COPD, AIDS and multiple-organ system failure), prior antibiotic therapy, invasive operations, and gene polymorphisms are the internationally recognized independent factors of VAP at present. Head trauma was the underlying diagnosis in 36.3% of those who developed late onset VAP in this study.

To determine predisposing factors, one would have to also have a control arm to compare against to see if whatever factor is being studied increases the probability of a patient developing VAP. In the absence a control arm, one therefore could not determine predisposing factors. The study does, however, illustrate the demographics of patients, to identify which of the known predisposing factors were found in this VAP population with COPD worth highlighting as 2 of the patients with an unfavourable outcome had COPD as a comorbidity.

As shown on Table 1, the male sex is a dominant characteristic making 75% of patients. The study identified comorbidities in 29.2% of the cohort. These comorbidities were of such a vast nature that none of them can be particularly identified as associated with development of VAP. Immunosuppression has been described as an independent risk factor, and 29.2% of patients are HIV positive, which can-not be ignored as having played a role in these patients development of VAP(17). The average length of ICU stay in this patient group is 15 days, with up to 6 ventilator days prior VAP diagnosis, with each day of ventilation contributing to the increased possibility of developing VAP(17).

Note-worthy is that advanced age did not play a role in this cohort as the median age was 40 years. A significant contributor to this maybe the fact that 37.5% of the patients were trauma patients who tend to be majority younger patients. In the context of a developing world with a limited number of critical care beds, it becomes an area of further research whether rationing does not play a role in the number of patients of advanced age in this ICU, even more so looking at the fact that the mean age in other studies from developing countries is around 55 years, and also noting that a previous South African study found no association between age and development of VAP (4,31,32).

Shown in Table 3.2 are the predisposing factors associated with development of multi drug resistant organism causing VAP in this population. These are airway access through tracheostomy (relative risk [RR] 1.68 (95% CI 0.78- 3.57) and with late-onset VAP – RR 2.36 (95% 0.95- 5.88).

The study demonstrates that a longer duration of admission prior to admission is associated with more infections with MDR organism as demonstrated on Figure 6, the average time to late VAP onset was 6 days. Airway access with a tracheostomy, is an independent risk factor(31). However, it must be kept in mind that the leading indication for a tracheostomy in

ICU patients is prolonged intubation for a period of at least 10 days. This means that these patients beyond just developing MDR VAP in association with having a tracheostomy, have also been admitted for longer than ten days.

At this point HIV is not shown to be a risk factor for developing MDR VAP as 33.3% of the population studied has an unknown HIV status. South Africa has a high HIV positive population, and this study was not powered to determine whether HIV positive patients require more ICU admission than HIV negative patients. Clinicians are encouraged to keep this in the back of their minds in treating HIV positive patients with VAP as it has a great impact on the choice of empiric antibiotics. Only one out of the twenty-five patients had a known HIV associated opportunistic infection (pulmonary tuberculosis) as the presumed cause of VAP. This is not a known common cause of VAP as the disease has a chronic rather than acute course. The South African population has a high prevalence of latent TB, as such, TB reactivation due to immune paresis from severe acute illness may be expected.

4.3 Pathogenic Organisms

An analysis of positive cultures from the admission period was carried out, especially those collected 48 hours before or after the diagnosis of VAP was made, with most interest on the organism isolated in blood cultures, tracheal aspirate, as well as pleural fluid aspirate. This opportunity was utilised to rule out other possible sources of sepsis in these patients, by looking at other culture specimen (urine, catheters tips, central lines and abdominal wash outs as well as tissue cultures sent during surgery), to see if an organism had grown and therefore suggest site of sepsis.

All the patients included in this study had no positive cultures from other sites to suggest an alternative source of the organisms. None of these patients had a para-pneumonic effusion and as such there is no data on pleural fluid aspirates. The positive cultures were stratified into early and late VAP looking at both tracheal aspirates and blood cultures for each group. Of 24 patients who developed VAP, 17 (70.8%) had an organism isolated from ETA specimens. The distribution of the organisms isolated are shown in Figure 2. 13 patients who had early-onset VAP, 7 (53.8%) had an organism isolated from ETA specimens while of 11 patients with late-onset VAP, 10 (90.9%) had an organism identified. The distribution of the organisms isolated by onset of VAP are shown in Figure 3. Of the 24 patients who developed VAP, 11 (45.8%)

had organism isolated on blood culture. Of these 11, 4 (36.4%) had early-onset VAP while 7 (63.6%) had late -onset VAP.

The most isolated pathogens are the Gram-negative bacilli (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*) comprising 53.6% of all isolates, with many of the patients have cultures positive of similar organisms on both blood cultures and tracheal aspirates. The other Gram-negative bacilli isolated were *Escherichia coli*, *Stenotrophomonas maltophilia*, *Citrobacter koseri* and *Proteus mirabilis* making up 14.2% of all aspirates, bringing the percentage total Gram-negative bacilli isolates to 67.8%. This is in keeping with what is observed throughout the world, including previous findings in the South African context, with Gram-negative bacilli making up approximately 60% of all isolates in VAP patients(3,4,9,13).

The second most common organism isolated was *Haemophilus influenzae* with 10.7% of isolates, this again is consistent with findings around the world(33). In this study, *Haemophilus influenzae* was isolated in early VAP only. This is in accordance with the knowledge that, prior antibiotic exposure is not a risk factor for respiratory infection with *Haemophilus influenzae*. In early VAP one would expect that majority at least of these patients have no prior antibiotic exposure. Rello et al noted in 1992 -that *Haemophilus influenzae* patient were co-infected with Gram-positive cocci, which was confirmed in this study where two thirds of the patients with *influenzae* were co-infected with *Staphylococcus aureus* (33).

Staphylococcus aureus also makes up 10.7% of all organisms isolated, two-thirds of which is from blood cultures. A third of these isolates are MRSA. In developing countries, *Staphylococcus aureus* makes up between 6 and 58% of VAP cases, with developed countries recording an average of 20%. The findings of this study fall within the expected ranges for developed countries(5,13). The isolates from early VAP samples were methicillin sensitive, again attesting to the fact that such patients would have had limited health care and antibiotic exposure prior to diagnosis of VAP. As discussed below, MRSA was associated with late VAP.

The least common infections were Mycobacterial and fungal infections comprising 1 case (3.6%) each. The mycobacterial infection was discussed above with that case occurring in the setting of HIV. It is important to note that this is not a typical causative organism for VAP,

and it may represent reactivation of latent TB due to immune paresis from acute illness. *Candida albicans* was the fungal organism isolated and this finding is comparable to world findings because 0.9% reported in the United States of America (USA) and up to 7% in developing countries are prevalence figures for candida VAP(13).

Another important concept in microbial aetiology of diseases is the sensitivity of those organisms as it has an impact on treatment options as well as disease outcome. The distribution of such organisms is also of importance between early and late VAP as it affects empiric antibiotics choice. The more susceptible organisms tend to occur in the early VAP group and the multi drug resistant ones are more prevalent in the late VAP population. These findings are to be expected, from what is known so far about the microbiology of VAP and strengthens the argument on the importance of the classification of VAP into early and late(1,15).

It is concerning that as early as 2014 there were already such high amounts of resistant organisms, a concern also shared by the CDC on their 2013 report on antibiotic resistance(34). Contrasting that against the worlds growing concern over the increase in the prevalence of antimicrobial resistance due to wide spread sometimes ill-advised antibiotic use means that by 2020 this does not correlate well with our current antibiogram(34,35). The known risk factors for VAP secondary to infection by resistant organisms include prior intravenous antibiotic use within ninety days, five or more days of hospitalisation prior to VAP, and acute dialysis prior to VAP.

In this cohort, many patients with MDR organisms have at least two of these risk factors, namely, number of days in hospital prior to VAP, and possible intravenous antibiotics in prior days, as these patients were in the late VAP group. As shown in Figure 6 above, the average number of days for the diagnosis of late VAP in was 6 days. In addition to that, One other factor was identified as possible risk factors for MDR organisms, being airway access via a tracheostomy. These findings have been discussed above in section 4.2.2 under the predisposing factors. It is important to note that, as far as tracheostomies are concerned there has been contrasting evidence as to whether they are protective or predisposing to VAP(31,36).

4.4 Patient outcomes

Of the 24 patient who had VAP, 7 (29.2%) died while the remaining 17 were discharged from ICU. This shows a mortality rate that is in the lower end of the reported mortality ranges so far. VAP carries high all-cause mortality rates ranging from 24 to 50% and this study is

within this range at 29.2%, in proximity with a previous South African report of 37.5% mortality (1,2,4). The majority of the mortalities were surgical patients 4 out of 7 (57%), 2 out of 7 medical and one patient with an unknown diagnosis, however 72% of patients with late VAP were surgical patients therefore explaining why they contribute more to mortality. Unfortunately, there was inconsistent documentation of severity scores for these patients and only 2 of the demised 7 patients had documented admission APACHE II scores at 21 and 26 respectively, with missing data in 54.4% of the patients. Because of this limitation we cannot say whether the severity of disease at admission played a major role in the outcome as compared to clinical decline in ICU related solely to VAP. It is noteworthy that there are at least 3 other patients with documented higher APACHE II scores who had a favourable outcome. The outcome of those patients who were discharged from ICU once they were transferred to the general ward is beyond the scope of this study.

Late-onset VAP is associated with much higher mortality compared to early-onset VAP 54.6% for late-onset VAP compared to 7.7% for early onset; X^2 p-value =0.018. This is likely due to two issues, one being that a long duration of stay in ICU of 6 days (average days to late VAP) is an indirect indication of severe illness. Also, as shown above, more resistant organisms were isolated in the late VAP group, therefore making management of these patients even more difficult. This again highlights the importance of differentiating early from late VAP.

Chapter 5

5 Conclusion

This study shows a low moderate prevalence of VAP of 16.4 events per 1000 ventilator days. Late onset VAP, as well as airway access via tracheostomy, are associated with infection with drug resistant organisms. The study also shows a VAP mortality of 29.2%, with the majority associated with late VAP, thus highlighting the importance of implementing preventative measures. A causative organism was isolated on culture in most, either of tracheal aspirates or blood, with Gram-negative bacilli being the most common. Clinicians are encouraged to develop antibiograms for their ICU units to guide empiric treatment. More research is required to assess the contribution of such factors as age, severity of illness, head, and chest trauma as well as degree of immunosuppression to the development and outcomes of VAP.

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7 Appendices

7.1 Annexure 1

Data collection sheet

Demographics

Patient study number

AGE(years)	
GENDER	☐ Male ☐ Female
RACE	A ☐ W ☐ C ☐ I ☐
Admission source	

Clinical information

Primary diagnosis	
HIV	Pos ☐ Neg ☐
CD4 (cell/ml ³)	
ARVs	Naïve ☐ current ☐ default ☐ unknown ☐

Clinical

Date of ICU admission	
Date of initiation of ventilation	
Mode of airway access	ETT ☐ Trachea ☐
Indication/s for mechanical ventilation	Airway protection ☐ Resp failure ☐ Other ☐
Oral care	Yes ☐ No ☐ unknown ☐



Antacids	Yes ☐ unknown	No ☐	☐
Sedation	Yes ☐	No ☐	Unknown ☐
Head elevation (°)			

APACHE II	SAPS II
SOFA	WBC
Neutrophil bands (at time of VAP diagnosis)	Neutrophil to lymphocyte ratio

Cultures

Culture	Status	Organism	Sensitivity
Blood			
ETA			
BAL			
Mini-BAL			
PSB			

History

Comorbidities

1.
2.
3.
4.

Recent hospitalisation ☐ yes ☐ no Date

Antibiotic Date Name..... Route..... Duration
.....days

Diagnostic criteria

Chest X-ray new infiltrate yes ☐ no ☐ unknown ☐

Purulent secretions yes ☐ no ☐

Date of VAP diagnosis	
Date of antibiotic (empirical)	
Antibiotic change	
Outcome	Discharged ☐ Died ☐
State at 30 days	Live ☐ Dead ☐ Unknown ☐

7.2 Ethics clearance certificate

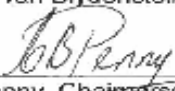
UNIVERSITY OF THE
WITWATERSRAND
JOHANNESBURG



R14/49 Dr Sibulele Mazwi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

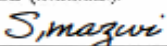
CLEARANCE CERTIFICATE NO. M190124

NAME: Dr Sibulele Mazwi
(Principal Investigator)
DEPARTMENT: Internal Medicine
Helen Joseph Hospital
PROJECT TITLE: Ventilator associated pneumonia in a Johannesburg
academic ICU
DATE CONSIDERED: 25/01/2019
DECISION: Approved unconditionally
CONDITIONS:
SUPERVISOR: Dr Alex van Blydenstein and Dr Murimisi Mukansi
APPROVED BY: 
Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL: 29/04/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed January and will therefore be due in the month of January each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).


Principal Investigator Signature

29/04/2019
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