Risk Factors and Treatment Patterns of Ventilator Associated Pneumonia in Intensive Care Patients at Kenyatta National Hospital

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DECLARATION

This dissertation is my original work and has not been presented for a degree in any university or published anywhere else.

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DEDICATION

To the love of my life, Leo, for believing in me, challenging and inspiring me to excellence and all the while being a wonderful father to our boys.

LIST OF ABBREVIATIONS

APACHE II	Acute Physiology And Chronic Health Evaluation II
ARDS	Acute Respiratory Distress Syndrome
CAP	Community Acquired Pneumonia
C-L	Cefepime- Levofloxacin
GCS	Glasgow Coma Scale
ICU	Intensive Care Unit
KNH	Kenyatta National Hospital
MBC	Minimum Bactericidal Concentration
MDR	Multiple Drug Resistance
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin Resistant *Staphyloccocus aureus*
MV	Mechanical Ventilation
PICU	Paediatric Intensive Care Unit
P-T-A	Piperacillin- Tazobactam- Amikacin
SPSS	Statistical Package for Social Sciences
VAP	Ventilator Associated Pneumonia

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ABSTRACT

Background: Ventilator associated pneumonia (VAP) is defined as nosocomial pneumonia in a patient on mechanical ventilatory support by endotracheal tube or tracheostomy for ≥ 48hours.[1,5] Studies show that VAP affects about eight to 20% of ICU patients and up to 27% of MV patients.[3,5,8] There are identified risk factors associated with VAP.[3,4,7]

The purpose of this study was to determine the extent of infection, risk factors and treatment patterns of critically ill patients at the Kenyatta National Hospital ICU.

Method: This was a hospital based prospective observational study in all patients admitted in the intensive care unit of Kenyatta National Hospital and put on mechanical ventilation for ≥ 48hrs in a period of four months from April to July 2009.

These patients were followed up daily for development of VAP. Potential risk factors for VAP were noted before development of VAP. The antibiotics chosen for treatment of VAP and the clinical outcome of the patient following treatment were evaluated. The data collected were analyzed using Statistical Package for Social Sciences (SPSS) software.

Results: Overall, 320 patients were admitted to the ICU for the study period, 139 of these were mechanically ventilated for ≥ 48 hours and only 39 were diagnosed to have VAP.

The incidence of VAP was 12.2% in this population, and 28% in the mechanically ventilated patients. The mean number of days to development of VAP was 8.7 ± 0.9.

The commonest bacterial pathogens isolated on tracheal aspirates were *Klebsiella* (23.1%), *Citrobacter* (12.8%), *Staphylococcus aureus* (12.8%), *Pseudomonas aeruginosa* (10.3%) and *Acinetobacter* species (10.3%).

The most commonly used class of antibiotics was cephalosporins (53.8%) and the main drug in this class was ceftriaxone (41%). Meropenem was the main antipseudomonal antibiotic used.

Conclusion: *Klebsiella* species was the commonest organism isolated. The key drugs used for the treatment of VAP were ceftriaxone and meropenem.

The commonest modifiable risk factors for VAP were enteral feeds and use of paralytic agents. Other common risk factors were low GCS, trauma, reintubation and sepsis.

Recommendations

- A further study involving a larger population is proposed to better document these findings.
- The KNH ICU team should be advised to identify patients who have modifiable risk factors early enough, to better their management.
- A more comprehensive antibiotic use review should be conducted in order to develop a formulary for treatment of VAP in the institution.

1.0 INTRODUCTION

1.1Background

Pneumonia is an inflammatory illness of the lung whereby the lung parenchyma/ alveoli are inflamed and there is abnormal alveolar filling with fluid. It can result from infection with bacteria, viruses, fungi or parasites and chemical or physical injury to the lungs or be idiopathic.[6] Pneumonia affects all age groups but it is more fatal in the elderly and chronically or terminally ill patients.

Ventilator Associated Pneumonia (VAP) is defined as nosocomial pneumonia in a patient on mechanical ventilatory support by endotracheal tube or tracheostomy for $\geq$ 48hours. [1,5] VAP can develop at any time during mechanical ventilation but most often in the first few days after intubation, as the intubation process itself and also the presence of the tube contribute to the development of VAP. If it occurs early, fewer resistant organisms are involved .[5,7] VAP arises when bacteria invade the pulmonary parenchyma in patients receiving mechanical ventilation (MV).[4] Inoculation of the bacteria is either from aspiration of secretions, colonization of the aerodigestive tract or use of contaminated equipment or medicines.[4] VAP results from infection flooding the air filled sacs (alveoli) in the lung that are responsible for absorbing oxygen from the atmosphere. [5]

VAP is one of the most common infections acquired by patients in critical care units.[2,9] Studies show that VAP affects about eight to 20% of ICU patients and up to 27% of MV patients.[3,5,8] VAP is associated with high mortality rates exceeding 10% and even up to 40%. [7]

Mortality is more likely when VAP is associated with certain microorganisms such as *Pseudomonas* and *Acinetobacter*, blood stream infections and ineffective initial antibiotics.[5] Chastre et al report that mortality can go up to 76% in some settings.[8] Considerable morbidity including prolonged ICU length of stay, prolonged mechanical ventilation and increased cost of hospitalization are common.[4,46] The length of ICU stay is found to be longer for medical than surgical patients with VAP.[46]

Some of the risk factors associated with VAP include pre-existing sinusitis, prolonged duration of mechanical ventilation, presence of chronic pulmonary disease, sepsis, witnessed aspiration, ARDS, neurological disease, trauma, prior use of antibiotics, enteral feeding, paralytic agents, extremes of ages and red cell transfusion.[3,4,7]. Risk factors for multidrug resistant (MDR) strains include ventilation for more than 5 days, recent hospitalization (in the last 90 days), residence in a nursing home, treatment in a hemodialysis clinic and prior antibiotic use (last 90 days).[7]

General strategies found to reduce the risk of VAP include conducting active surveillance, hand hygiene, use of non invasive ventilation, minimizing duration of ventilation, assessing daily readiness to wean off the ventilator and personnel education.[4] To prevent aspiration, the patient should be in semirecumbent position (30 to 45 degree elevation of the head of bed) if possible, avoid gastric overdistension, avoid unplanned extubation and reintubation and use cuffed endotracheal tube. To reduce colonization of the aerodigestive tract, orotracheal intubation is preferred to nasotracheal intubation which increases the risk of sinusitis hence that of VAP. Acid suppressive therapy such as H2 blockers and proton pump inhibitors increase colonization density of the aerodigestive tract. Oral care is crucial to minimize risk of VAP. Sterile water should be used to rinse reusable respiratory equipment to minimize contamination.

Patients on MV are often sedated and rarely are able to communicate hence many of the typical symptoms of pneumonia will either be absent or cannot be obtained. [5] Such symptoms include cough, chest pain, fever and difficulty in breathing. [6] Absence of these symptoms complicates the diagnosis of VAP and isolation of potential pathogens from endotracheal secretions may not necessarily reflect flora of the lower respiratory tract.[7] Hence, the important symptoms in VAP patients are fever, low body temperature, new purulent sputum and hypoxia. [5] Diagnosis is thus a combination of radiological and clinical criteria.[5,7]

Vidaur *et al* declare a clinical diagnosis based on new pulmonary opacity and purulent respiratory secretions plus other signs of inflammation as valuable in screening patients suspected with VAP. [9,17]

Rea-Neto and colleagues performed a systemic review of literature on diagnosis of VAP.[3] They confirmed the fact that there is no single clinical manifestation that can be used alone to diagnose VAP. Chest radiology was reported to be typically non-specific though very sensitive. Clinical criteria used in combination may be helpful in diagnosing VAP but interobserver variability and the moderate performance should be considered. Bacteriological data do not increase the accuracy of the diagnosis as compared to the clinical diagnosis.

Rea- Neto gives different clinical criteria used in diagnosing VAP, including the Johanson criteria, the Clinical Pulmonary Infection Score (CPIS) and the Center for Disease Control and Prevention (CDC) criteria. In this study, I have borrowed mainly from the CPIS criteria. This is consistent with a previous study by Garrard S C and A'Court D C.[59]

Pathogenesis

The microorganisms responsible for VAP differ from those causing community acquired pneumonia (CAP). Viruses and fungi are however rare in people without underlying immune deficiencies. [5] In the community, S*treptococcus pneumoniae*, *Haemophilus influenzae* or S*taphylococcus aureus* are common whereas P*seudomonas* species is the major organism in hospital acquired pneumonia regardless of ventilation.

Though any organisms causing CAP can cause VAP, several multiple drug resistant (MDR) organisms are important. *Pseudomonas aeruginosa* is a MDR gram negative bacterium causing VAP which has natural resistance to many commercially available antibiotics and acquires resistance through up regulation or mutation of a variety of efflux pumps which pump antibiotics out of the cell.

The organisms may form biofilms resistant to drugs and host defense mechanisms.[7] Other bacteria causing VAP include *Klebsiella pneumoniae, Serratia marcenscens, Enterobacter* group, C*itrobacter, Acinetobacter* and *Methicillin Resistant Staphylococcus aureus (MRSA).* [5,6]

Certain patient characteristics can indicate the causative pathogen for VAP: *H. influenzae* in patients with chronic lung disease, *S. aureus* in the elderly, diabetic, renal failure, head injury, neurosurgery or recent influenza. [7] Etiological agents widely differ in different populations of patients in ICUs, and with duration of hospital stay and prior antibiotic use. [5,6,7,8]

Probable organisms in Kenyatta National Hospital intensive care unit.

A literature search shows that very little work on ventilator-associated pneumonia has been done in Kenya. However, a preliminary survey at the KNH intensive care unit's culture and sensitivity

results shows that the most probable pathogens responsible for VAP include *Pseudomonas aeruginosa, Staphylococcus aureus*, *Klebsiella* species and *acinetobacter* species.

Pathophysiology

Many bacteria live in parts of the upper respiratory tract such as the nose, mouth, or sinuses and can be inhaled.[6] An endotracheal or tracheostomy tube allows free passage of bacteria into the lower segments of the lung.[5]

Other bacteria colonize the endotracheal tube or tracheostomy tube and are embolised into the lungs with each breath. Procedures such as deep suctioning or bronchoscopy may push down bacteria in to the lungs.

Bacteria then invade intercellular and interalveolar spaces through connecting pores triggering the immune system to send neutrophils to the lungs.[6] Neutrophils then engulf and kill the offending organisms and also release cytokines causing a general activation of the immune system. This leads to fever, chills and fatigue. The neutrophils, bacteria and fluid from the surrounding blood vessels fill alveoli and interrupt normal oxygen transportation. Bacteria may travel to the blood stream causing fatal illnesses such as septic shock, low blood pressure and multiple organ damage. Bacteria can get into the pleural cavity and cause empyema.

Treatment

When VAP is suspected, broad spectrum empirical antibiotics should be started urgently until a particular bacterium and its sensitivities are determined. [5,7] Empirical treatment should consider risk factors of the patient for resistance and the local prevalence of resistant microbes. [5] It also considers time of onset of illness therefore the likely pathogens, previous antibiotic use, severity

and speed of progression of illness, local pathogens and resistance patterns and other patient related factors such as renal and hepatic impairment.[7]

Therapy should change when the causative agent is known and continue until symptoms resolve (seven to fourteen days).[7] Possible antibiotic combinations include:

- Vancomycin/linezolid and ciprofloxacin
- Cefepime and gentamicin/amikacin/tobramycin
- Vancomycin/linezolid and ceftazidime
- Ureidopenicillins and beta lactam inhibitors piperacillin/tazobactam/ticarcillin/clavulanic acid
- Carbapemens (imipenem/meropenem).

In patients who have not used antibiotics before, the most likely organisms are gram positive cocci in early infection or aerobic gram negative bacilli in late infection.

1.2 Problem Statement

VAP is one of the commonest infections acquired by patients in ICUs who are receiving mechanical ventilation, either by endotracheal or tracheostomy tubes. Current studies report rates of VAP that range from one to four cases per 1000 ventilator days, with higher rates in some neonatal and surgical patient populations.[4] VAP is a cause of significant patient morbidity and mortality and increase cost of health care by extended hospitalisation, excessive use of antibiotics and other medical costs.[4,7]

The pathogenesis of VAP is due to bacterial invasion of pulmonary parenchyma in patients on MV. Strategies to prevent VAP target the three common mechanisms by which it develops, which are aspiration of secretions, colonisation of the aerodigestive tract and use of contaminated equipment.[4] Quality improvement initiatives suggest that many cases of VAP might be prevented by careful attention to the process of care.

Even though there are several international publications, [3, 9, 11, 13, 14, 15, and 16] that have attempted to discuss the challenges of diagnosis and treatment of VAP and also the pathogenesis, little is known about VAP in developing countries, including Kenya. Furthermore, better understanding of the risk factors and patterns of management of VAP will be helpful in better designing of preventive and therapeutic strategies in the future.

1.3 Study Justification

Active surveillance is necessary to accurately identify patients with VAP. Early diagnosis and management of VAP is important to reduce the adverse effects of the disease in terms of mortality and morbidity and the complications that may arise such as acute lung injury, multiple organ dysfunction and respiratory decompensation.[7]

This study addressed the problems associated with VAP by determining the extent of this disease and the risk factors that led to its development in KNH intensive care unit. The findings will hence contribute as a basis for improving and possibly developing guidelines and policies on proper and prompt treatment and prevention of VAP in this setting.

2.0 LITERATURE REVIEW

Bacteriology and incidence

Awareness of microbiology of VAP is essential for selecting optimal antibiotic therapy and improving outcomes.[16] The bacterial pathogens are usually colonisers of the oropharynyx or gut or transmitted from the environment or other patients by the health care workers. The common bacterial pathogens are P*seudomonas* species, *Staphylococci, Enterobacteriaceae, Streptococci, Haemophilus* among others. These pathogens vary depending on patient characteristics and certain clinical circumstances but differ mainly due to primarily the duration of mechanical ventilation and /or degree of prior antibiotic exposure and also the geographical location.

The duration of mechanical ventilation prior to onset of VAP and recent (within 15 days) use of antibiotics are two key factors favouring emergence of potentially resistant organisms responsible for VAP, mainly *Pseudomonas aeruginosa,* Acinetobacter species and MRSA.[16,42,53]

A study by Heyland *et al* revealed that the length of ICU stay was longer for patients with high risk organisms (*Pseudomonas* species, *Acinetobacter* species, *Stenotrophomonas* and MRSA) than others which are considered low risk.[46] However, it is worth noting that potentially multiresistant pathogens are the most common isolated in both early onset and late onset VAP, with no significant difference noted for the pathogenesis of the two types.[49]

One study by Akca *et al* found out that *Pseudomonas aeruginosa* was the commonest cause of VAP (33% of 260 patients in the study). The others were MRSA, *Acinetobacter* species and other non-resistant species in that order.[17]

Namiduru *et al* also determined that the commonest pathogen for VAP was P*seudomonas* (33.9%) followed by *S. aureus* (30%), *Acinetobacter* (26.1%) and *Enterobacter* species (4.3%).[25]

In a retrospective study by Teixeira *et al*, MDR bacteria caused 82.4% of the VAP in their setting.[24] *Staphylococcus aureus* was responsible for 27.5% and P*seudomonas* for 17.6% of the VAP. The majority was late onset VAP (63.7%) rather than early onset. MDR VAP was responsible for 61.3% of the mortality.

A study by Cook *et al* showed the average number of days after admission that patients develop VAP was 9.0 ± 5.9 days. [12]

In Latin America, a study carried out in three ICUs in a 550 bed University hospital, showed that 22% of the patients on MV developed VAP in 5.9 ± 3.6 days after admission and overall incidence was 29 cases per 1000 ventilator days.[23]

In Kenya, a study was conducted in the ICU of the Kenyatta National Hospital (KNH) and it showed that out of the 195 patients admitted to the unit during the study period, 137 (70.3%) received antibiotics commonly Meropenem, Ceftazidime, Cefuroxime, Vancomycin, coamoxiclav (amoxicillin with clavulanic acid) and Metronidazole for treatment of VAP and other bacterial infections in the ICU.[20] Common bacteria isolated from tracheal aspirates, urine and blood were: *Pseudomonas, Klebsiella, Citrobacter, S. aureus, S. pneumonia* and *Acinetobacter* among others. However, this study did not address the issue of risk factors and detailed diagnosis and treatment patterns of VAP to be able to make any tangible conclusions or even derive evidence-based conclusions to help better design innovative and appropriate therapeutic care in future.

Risk factors

The attributable risk of VAP appears to vary with patient population and the infecting organism.[46] Being able to define the risk for development of VAP may help clinicians anticipate it and researchers to study the potential interventions in patients at highest risk.[11,55]

The risk factors for development of VAP can be either fixed such as underlying cardio-respiratory disease, neurological injury and trauma, or modifiable risk factors such as supine body position, witnessed aspiration, paralytic agents and antibiotic exposure.[45] The modifiable risk factors therefore represent effective VAP prevention strategies.

A study by Giard *et al* showed that the risk factors for early onset VAP and late onset VAP were different hence the need for specific preventive measures.[48] They define early onset VAP as one occurring $\leq$ 6 days after intubation whereas late onset developed after more than 6 days of MV. This study reported the major independent risk factor for early onset VAP as a surgical diagnostic category whereas for late onset were older age, higher APACHE II score, infection on admission, another nosocomial infection before VAP and exposure to central venous catheter before VAP. Akca *et al* identified the risk factors for early onset VAP with multiresistant pathogens to be emergency intubation, aspiration and a Glasgow Coma Scale (GCS) of 10 or less.[52] The GCS is a commonly used standardised test for evaluating brain injuries. It rates three categories of patient responses: Eye opening (E), best Motor response (M) and best Verbal response (V). Levels of response indicate the degree of nervous system or brain impairment. Summed GCS score = E + M + V (3-15)

In 1998 Cook *et al* sought to define risk for VAP. They found that the risk increased each day on ventilation until day five but decreased later. [11] Some of the risk factors they identified in the study were admitting diagnosis of burns, trauma, CNS disease, respiratory disease, cardiac disease, recent MV, witnessed aspiration and use of paralytic drugs. Exposure to antibiotics decreases risk by almost two thirds. [7,11]

Akca *et al* concluded that patients who had undergone emergency intubation, thoracic trauma, aspiration, head trauma are at significantly higher risk of developing VAP and should be rigorously observed.[17]

Antibiotic resistant pathogens such as *Pseudomonas, Acinetobacter* and MRSA are more common after prior antibiotic treatment or prolonged hospitalisation or MV and when other risk factors are present. [16] Prior use of ceftazidime has been associated with infection with resistant strains of *Acinetobacter* species.[57]

Eleni *et al* studied the incidence of risk factors associated with development of VAP. Ventilator Associated Pneumonia occurred in 32% of the patients in this study and the risk factors included bronchoscopy, tube tracheostomy, APACHEII score of $\geq$ 18 and enteral feeding. [18] APACHE II score (Acute Physiology and Chronic Health Evaluation) is a disease severity classification system used to assess the severity of illness for critically ill patients in the ICUs. It provides an estimate of ICU mortality based on a number of laboratory values and patient signs taking into account both acute and chronic disease.

The data used should be from within 24 hours of ICU admission and the worst values (furthest from baseline or normal) should be used.[59] After admission of a patient to an intensive care unit, an integer score from 0 to 71 is computed based on several measurements; higher scores imply a more severe disease and a higher risk of death.

A study conducted in a PICU, showed the rate of VAP as 10.39 per 1000 ventilator days.[21] Increased rates were associated with black race, seizures, transplant, burns, congenital immunodeficiency, respiratory arrest, cardiopulmonary arrest, transfusion and sepsis. VAP increased the length of stay in PICU and mortality rate.

In another study, Elatrous prospectively followed up 73 patients to determine incidence and risk factors for VAP and found out that 38% of MV patients in the eight- bed ICU developed VAP with incidence of 46 episodes per 100 patient ventilator days. [22] The risk factors were multiple intubations during MV, enteral feeding and depressed level of consciousness.

Treatment

Optimal antimicrobial treatment of VAP is important since inadequate therapy is consistently associated with increased mortality.[28,47,50] However, excessive antimicrobial therapy leads to unnecessary treatment-related complications and costs and further increase prevalence of antimicrobial resistance.[29,47,50,54]

An adequate initial antimicrobial regimen should be selected before microbiology results become known, but likely pathogens and their resistance patterns predicted based on

published guidelines, patient factors and local epidemiologic data.[27] The initial empiric regimen must be broad spectrum and can be narrowed or discontinued as culture and susceptibility results permit.[15,27,50]

One of the challenges of antimicrobial treatment of VAP is that, regardless of availability of many safe drugs with well-understood pharmacokinetic and pharmacodynamic properties, the selection of therapy is complex.[27] This is mainly due to the diversity of microbial causes of VAP,[8,27] the increasing resistance among these pathogens,[30,31,32] delays in receiving definitive microbiological and susceptibility reports and pressure to avoid excessive antimicrobial drug use.[29]

Studies have consistently shown that adequate initial antimicrobial therapy for VAP lowers mortality rates[33-41] and even changing to appropriate therapy after culture results may not reduce this risk of mortality.[34,35,36]

The antimicrobial therapy has to be both appropriate and adequate to obtain the desired therapeutic outcome. Park defines 'appropriate' therapy as when the target pathogen is susceptible to the chosen drug, whereas an 'adequate' therapy means the appropriate drugs are selected, given in optimal dosages, by the correct route, in effective combinations and for the appropriate duration.[27] He further describes a de-escalation strategy that has evolved to address the challenges of treatment for VAP. This strategy involves aggressive broad spectrum initial empiric antimicrobial therapy, followed by narrowing or discontinuation of the drugs after microbial susceptibility results and the clinical course of the disease.[27,56]

In this approach, microbial samples are collected as soon as VAP is suspected, but therapy is initiated promptly and chosen to cover all the likely pathogens.

Giantsou *et al* report that for patients who have had appropriate treatment and shown a favourable clinical response, mortality and duration of ICU stay can be further improved by de-escalation therapy. [51]

In early onset VAP with no risk factors for MDR pathogens, antimicrobial-sensitive pathogens are likely and the empiric initial therapy can be provided by simple monotherapy using an antipseudomonal third generation cephalosporin, antipneumococcal flouroquinolone or ampicillin/sulbactam.[46] In late onset VAP, or if risk for a MDR pathogen is present, broad spectrum antimicrobial combinations are given.[42,50]

Bowton *et al* noted in their study that delayed administration of adequate antibiotic therapy is linked to an increased mortality rate.[15] According to this study, eight days of antibiotic therapy appeared equivalent to 15 days except for nonlactose-fermenting gram-negative organisms where longer duration of treatment reduced the risk of recrudescence after discontinuation of antibiotic therapy.

Chastre *et al* concurred to the above finding in their study where they compared eight versus 15 days of antibiotic therapy. [19] There was comparable clinical effectiveness against VAP with both regimens, the only advantage with the eight day regimen was that there was less antibiotic use

and among those who developed recurrent infections, multiresistant pathogens were less frequent in this group. This supports the theory of minimising the duration of therapy for VAP.

The recommended duration of therapy for VAP has been long: minimum seven to ten days for susceptible *Hemophilus* or *Staphylococcus* infections, and 14 to 21 days for more typical cases.[43] The optimal duration of therapy remains unknown,[27] though several studies have evaluated arbitrary courses ranging from three days to several weeks mostly based on clinical response.[44,45,46,47] Most of these approaches aim to reduce the antimicrobial exposure.

In an Indian study by Ahmed *et al* on 879 patients admitted in an ICU to compare treatment of VAP with Piperacillin-Tazobactam-Amikacin combination (P-T-A) versus Cefepime-Levofloxacin combination (C-L). [14] For the C-L group of patients, the duration of MV was shorter (five to eight days) compared to the P-T-A group (six to eleven days) and also the mean duration of ICU stay was reduced in the C-L group. A combination of C-L is found to be highly effective against P*seudomonas, E. coli* and *S. aureus.*

Ibrahim *et al* evaluated the use of a clinical guideline for the initial administration of adequate antimicrobial treatment for VAP. [46] The results showed that the use of a guideline increases administration of adequate treatment and decreases the overall duration of antibiotic use. This study hence suggests that similar types of guidelines employing local microbiologic data can be employed to improve overall antibiotic utilization for the treatment of VAP.

2.1 Goal of Study

To determine the extent of infection and improve management and prevention of ventilator associated pneumonia at Kenyatta National Hospital.

2.2 Objectives

2.2.1 General

To determine the risk factors associated with VAP and treatment patterns used for its management.

2.2.2 Specific

1. To identify the common pathogens causing VAP in mechanically ventilated patients admitted in the ICU at KNH and their sensitivity patterns.
2. To assess which of the established risk factors for development of VAP are present in the study population.
3. To determine the antibiotics used to treat VAP and their regimens, and the therapeutic outcome in these patients.

2.3 Research Questions

1. What are the most common pathogens causing VAP in the KNH ICU and what are their sensitivity patterns?
2. Which risk factors responsible for development of VAP are present in these patients?
3. What are the antibiotics chosen for managing VAP patients in this ICU and how are they used?
4. What is the clinical outcome of patients with VAP treated with specific antibiotics?

3.0 DESIGN AND METHODOLOGY

3.1.0 Study Design

A prospective observational study was conducted in the Kenyatta National Hospital (KNH), Critical/ Intensive Care Unit. The study population included all patients admitted to the ICU during the study period (from April to July 2009) who were put on mechanical ventilation for ≥ 48 hrs. Since the entire ICU population was considered to get those put on mechanical ventilation for ≥ 48 hrs, no sampling was done.

3.1.1. Inclusion Criteria

All patients admitted in the ICU who received MV for ≥ 48hrs and subsequently developed VAP according to the criteria used to diagnose VAP in the ICU-KNH.

3.1.2 Exclusion Criteria

Patients whose life expectancy was less than two days.

3.2 Ethical Considerations

Approval to carry out the study was obtained from Kenyatta National Hospital Ethics and Research Committee (Appendix 2)

There was no direct benefit to patients in the study. Future patients may benefit as the results from the study may be used for recommending better prevention and management of VAP in the hospital.

There were no risks to the patients during the study. Matters of concern in patient management were communicated in line with standard professional practice.

Confidentiality was attained by using study numbers and register numbers. All information obtained was confidential and only used for intended purposes. Patient names were not entered into the data collection form. The data collected were stored securely in password restricted files. A separate code list was maintained until data collection was complete.

3.3 Procedure and Data Collection Method

Ethical approval to carry out the study was obtained. All patients admitted to the ICU during the study period and put on mechanical ventilation for $\geq$ 48 hours were followed up for development of VAP.

A validated and reliability determined tool (Appendix 1) was used to collect pertinent data from patients inpatient files, treatment sheets and laboratory culture and sensitivity reports. The patients' biodata and admission details included age, sex, and admission diagnosis.

Potential risk factors for VAP noted before development of VAP were extracted from the patients' inpatient records and entered into the data collection tool.

The patients were then prospectively followed up and monitored daily for development of suspected VAP using the diagnostic criteria determined by the investigator from relevant literature review.

Once the results for organism isolation, culture and sensitivity were available from the microbiology laboratory, the information was extracted and entered into the data collection tool.

The number of days on MV before development of VAP was noted and entered into the data collection tool.

Patients were considered to have VAP only when they met the clinical criteria and the endotracheal aspirate culture was positive for bacteria 48 hours or more after initiation of MV.

The antibiotics chosen for treatment of VAP in each patient were extracted from the treatment sheets and entered into the data collection tool with the details of choice of drugs, dosing, frequency and duration of therapy.

The clinical outcome of the patient following treatment was evaluated.

3.4 Data Analysis Procedure

The data collected were transferred into a Microsoft Access database and analyzed using SPSS software. Descriptive statistics were used to summarise the results into means, medians and proportions. Results were also presented using frequency distribution tables and graphs.

3.5 Limitations of the Study

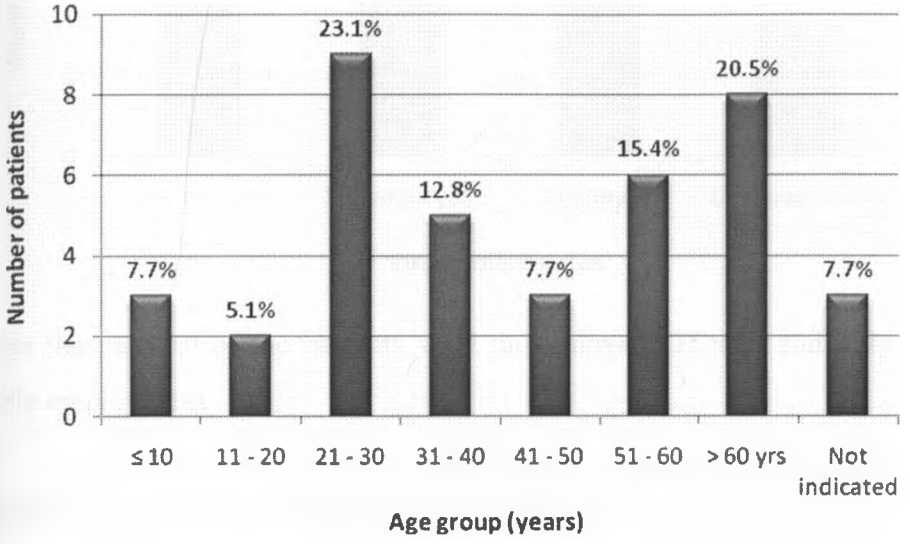
This being a single centre with a bed capacity of twenty, generalisation of the results may be limited.

The study was carried out for four months only; a longer duration would give a more comprehensive picture. The fact that currently there is no gold standard for diagnosis of VAP and poor documentation of the condition in this unit was also a limitation.

4.0 FINDINGS

4.1 DEMOGRAPHIC CHARACTERISTICS

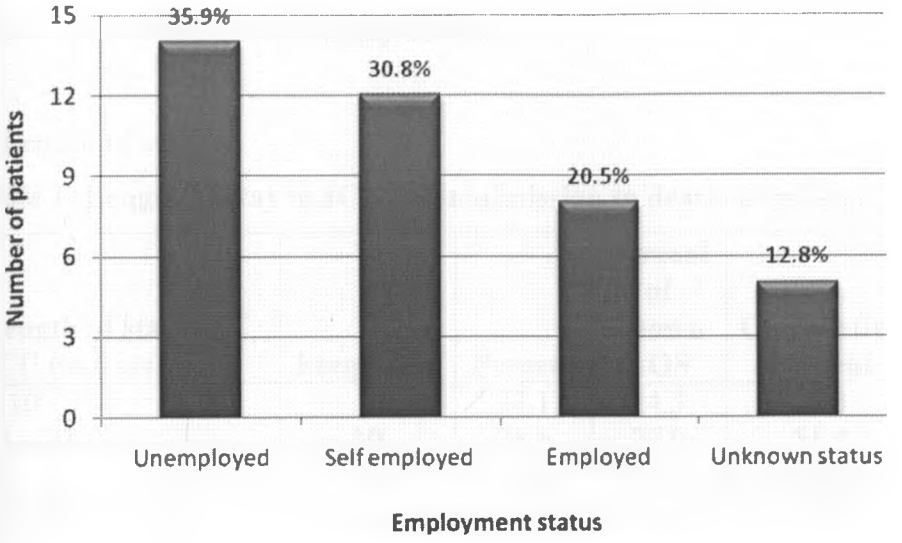
Figure 1: **Distribution of patients by age group**



The largest groups of patients included in this study were aged 21-30 years (23.1%) or above 60 years old (20.5%). (Mean=41.4 ± 6.9yrs, min=1, max=85, range=84, median=38.5yrs).

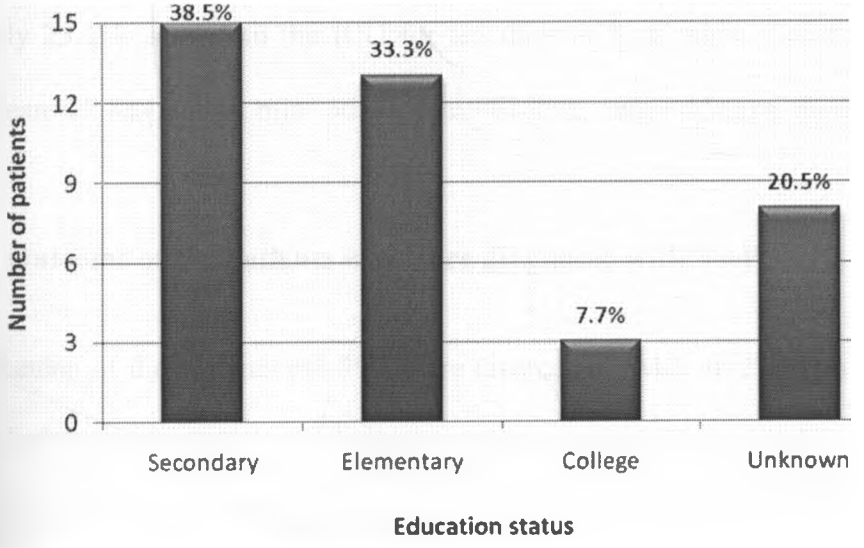
Twenty seven patients were male (69.2%) while twelve (30.8%) were female.

Figure 2: **Employment status of patients in the study**



More than a third of the patients were unemployed (35.9%) and only a fifth (20.5%) were in stable employment.

Figure 3: **Education status of patients in the study**



A minimal number of patients had college education (7.7%) while majority were of elementary (33.3%) and secondary (38.5%) levels.

4.2 HOSPITALIZATION

4.2.1 Admission and ICU stay Details

a, Length of stay

Table 1: **Length of stay in ICU from admission to death/ discharge**

Length of stay in ICU (in days)	Frequency	Percent	Percent of known LOS	Cumulative Percent
≤ 10	9	23.1	24.3	24.3
11 - 20	10	25.6	27.0	51.4
21 - 30	10	25.6	27.0	78.4
31 - 40	4	10.3	10.8	89.2
41 - 50	1	2.6	2.7	91.9
51 - 61	3	7.7	8.1	100.0
Still in the ICU (>80 days)	2	5.1		
Total	**39**	**100.0**	**100.0**	

Key: LOS= length of stay

Only 23.1% stayed in the ICU for ten days or less, while majority stayed for 11 to 30 days. (Mean=22.8±4.8days, min=6days, max=61days, range=55days, mode=23days, median=20days).

***b*, Outcome of the patients who were diagnosed with VAP**

Nineteen of the patients (48.7%) were discharged, with 46.2% dying while still in ICU. By the end of the study period, two long stay patients were still admitted in the unit.

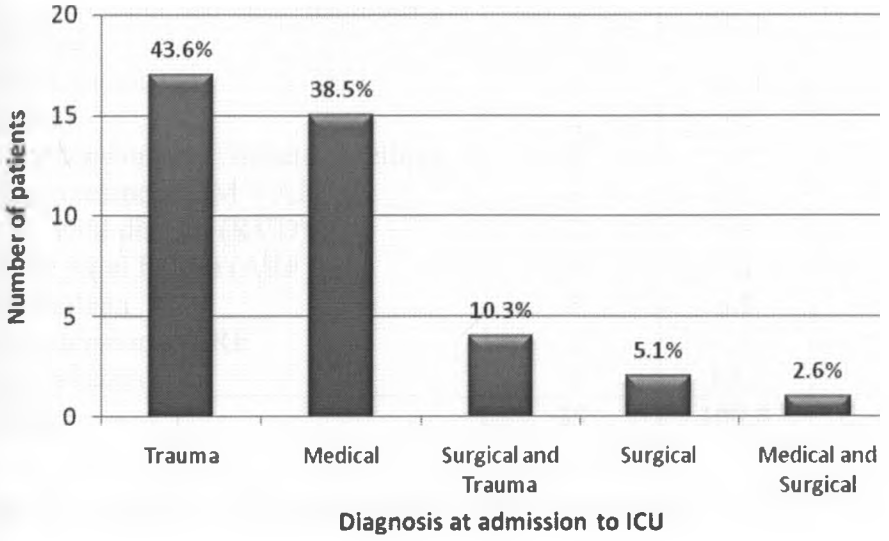
c, Type of intubation used for mechanical ventilation

Seventy seven percent (30) of the patients were on orotracheal while 23.1% (nine) were on tracheostomy type of intubation by the time VAP was diagnosed.

Most of the patients were on mechanical ventilation for the entire length of stay in ICU.

4.2.2 Diagnosis at admission to ICU

Figure 4: **Categories of patients admitted**



A big proportion of the patients (43.6%) were diagnosed as trauma cases during admission to ICU, 38.5% were medical cases.

Table 2: **Primary diagnosis at admission to ICU**

Primary diagnosis	Frequency	Percent
Severe head injury/ multiple injuries secondary to RTA or assault	19	48.7
Neurological disease (convulsions, GBS, meningitis, hemorrhagic CVA)	12	30.9
Septic shock/infections	4	10.3
Diabetic Ketoacidosis	1	2.6
Malignancy	1	2.6
HELLP	1	2.6
Poisoning	1	2.6
Total	**39**	**100**

Key: RTA= road traffic accident, HELLP= Hemolysis Elevated Liver Enzymes and Low Platelets syndrome

Majority of patients had injuries from road traffic accidents or due to assault (48.7%) being the reason for admission to ICU.

Table 3: **Secondary diagnosis at admission or during ICU stay**

Secondary diagnosis	Frequency	Percent
None	14	35.9
Pneumothorax and other respiratory diseases	4	10.3
Hypertension	4	10.3
Sepsis	2	5.1
Hypertension and Diabetes Mellitus	2	5.1
Hypertension + DM + ARF	2	5.1
Retroviral disease (RVD)	2	5.1
Acute renal failure (ARF)	2	5.1
Alcoholism	2	5.1
Hypertension + ARF	1	2.6
Not indicated	4	10.3
Total	**39**	**100.0**

Key: DM= Diabetes Mellitus, ARF = acute renal failure.

Fourteen (35.9%) of the patients had no secondary diagnosis while the rest had varied diagnoses.

Hypertension was common, either alone or in combination as a secondary diagnosis.

4.3 RISK FACTORS CONTRIBUTING TO DEVELOPMENT OF VAP

Table 4: **Risk factors observed in the patients who developed VAP**

Risk factor	Frequency	Percent
Enteral feeds	39	100.0
Paralytic agents	38	97.4
Low GCS	29	74.4
Trauma (thoracic/head)	20	51.3
Reintubation	13	33.3
Sepsis	11	28.2
Neurological disease	10	25.6
Witnessed aspiration	6	15.4
ARDS	6	15.4
Chronic pulmonary disease	1	2.6
Recent MV	1	2.6

It was observed from the study that enteral feeds was the leading risk factor for development of VAP as it was exhibited by all the patients while 97.4% was due to paralytic agents.

4.4 IDENTIFICATION OF VAP

4.4.1 Diagnosis of VAP

Table 5: **Number of days patients were on mechanical ventilation (MV) before developing VAP**

No. of days to VAP	Frequency	Percent	Cumulative Percent
≤ 5	16	41.0	41.0
6 - 10	10	25.6	66.7
11 - 15	8	20.5	87.2
16 - 20	4	10.3	97.4
21 - 25	1	2.6	100.0
Total	**39**	**100.0**	

A big proportion of the patients in the study (41%) developed VAP within five days, the number then tapers off with increase in days. (Mean=8.7 ± 1.7days, min=3days, max=24days, range=21days, mode=5days, median=7days).

Type of VAP

Slightly more than half (56.4%, 22) of the patients had late onset VAP while 43.6% (17) had early onset VAP.

Table 6: **Clinical Criteria for identification/diagnosis of VAP**

	Fever > 38°C		Purulent Sputum		Low body temperature		Hypoxia		WBC<4 or >10	
Response	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Yes	39	100.0	39	100.0	11	28.2	38	97.4	29	74.4
No	0	0.0	0	0.0	28	71.8	1	2.6	10	25.6
Total	**39**	**100.0**	**39**	**100.0**	**39**	**100.0**	**39**	**100.0**	**39**	**100.0**
Chi2	N/A		N/A		7.41		35.1		9.26	
df					1		1		1	
p					0.006		<0.001		0.002	

(Chi2=24.64 df=1 p<0.001)

From the clinical criteria used all the 39 patients exhibited fever of > 38°C and new purulent sputum; these were combined with the other criteria to varying levels.

Radiological criteria

Majority of patients (89.7%) did not meet the radiological criteria for VAP diagnosis.

4.4.2 Microscopic Culture and Sensitivity: Tracheal Aspirate

Table 7: **Organisms isolated from the tracheal aspirates of the patients with VAP**

Organism isolated	Frequency	Percent
Klebsiella spp.	9	23.1
Citrobacter spp.	5	12.8
Staphylococcus aureus	5	12.8
Acinetobacter spp.	4	10.3
Pseudomonas aeruginosa	4	10.3
Enterobacter spp.	2	5.1
Pseudomonas + Citrobacter	2	5.1
Pseudomonas + Proteus	2	5.1
Escherichia coli	1	2.6
Acinetobacter + Klebsiella	1	2.6
Klebsiella + Candida	1	2.6
Klebsiella + NGF	1	2.6
Pseudomonas + Klebsiella + Citrobacter	1	2.6
Pseudomonas + Klebsiella	1	2.6
Total	**39**	**100**

Key: NGF =non glucose fermentor

Klebsiella spp. was the commonest organism (23.1%), followed by *Citrobacter, Staphylococcus aureus, Acinetobacter* and *Pseudomonas aeruginosa.*

Thirty three percent of the patients sampled had unspecified quantities of isolated organisms, 28.2% had light growth of the organisms, 20.5% had moderate growth while 17.9% had heavy growth of the isolated organisms.

It was observed that MICS and MBCs were not done on the samples taken for culture and sensitivity testing.

Table 8: **Sensitive antibiotics by isolated organisms**

Antibiotic	Organism isolated										Total isolates sensitive
	Kleb-siella	*Pseudo-monas*	*Staphy-lococcus*	*Citro-bacter*	*Acineto-Bacter*	*Proteus*	*Entero-bacter*	*Candida*	*E. coli*	*NGF*	
Meropenem	10	9	1	7	1	1	2	1		1	**33**
Gentamicin	6	5	2	2	2	1					**18**
Imipenem	3	1	1	1	1			1			**8**
Amikacin	1	5		4	2		1				**13**
Ceftazidime	6	6	1	2	1						**16**
Ciprofloxacin	6	2		2	2				1		**13**
Coamoxiclav	2		1	1	1	1					**11**
Pip/tazobactam	1	5		2		1	1				**10**
Cefuroxime	5	1	3			1					**10**
Doxycycline		1	3	1					1		**6**
Ceftriaxone	1	1		1							**3**
Levofloxacin	1	1	1								**3**
Minocycline	2	1		2							**5**
Chloramphenicol	2				1						**3**
Norfloxacin					1	1					**2**
Azithromycin			1								**1**
Cefadroxil		1									**1**
Cefepime	2										**2**
Cefotaxime					1						**1**
Erythromycin			2								**2**
Oxacillin			3								**3**
Vancomycin			3								**3**
Total antibiotics sensitivity	**14**	**13**	**12**	**11**	**10**	**6**	**3**	**2**	**2**	**1**	

Table 9: **Resistant antibiotics by isolated organisms**

Antibiotic	Organism isolated										Total isolates resistant
	Kleb-siella	*Acineto-bacter*	*Citro-bacter*	*Pseudo-monas*	*Entero-bacter*	*Candida*	*E. coli*	*NGF*	*Proteus*	*Staphylo-coccus*	
Ceftazidime	6	3	5	3	2	1	1	1	2		**24**
Cefuroxime	5	2	3	3	1		1	1		1	**17**
Ceftriaxone	4	2	4	3	2	1	1				**17**
Coamoxiclav	6		5	3	1	1	1			1	**18**
Gentamicin	1	2	3	2	1	1	1				**11**
Ampicillin	2	2		1				1			**6**
Ciprofloxacin	1	1	2		1						**5**
Imipenem	3	1	1	3							**8**
Piperacillin/ tazobactam	2	2	1			1					**6**
Amikacin	1		1						1		**3**
Cefotaxime			1	1					1		**3**
Cotrimoxazole	1			1				1			**3**
Meropenem		2							1	1	**4**
Chloramphenicol	1	1									**2**
Doxycycline	1										**1**
Erythromycin										1	**1**
Levofloxacin			1								**1**
Tetracycline		1									**1**
Total antibiotics resistant	**14**	**11**	**11**	**9**	**6**	**5**	**5**	**4**	**4**	**4**	

4.5 TREATMENT OF VAP

4.5.1 Design of Dosages of Antibiotics

Majority (61.5%) of the patients were given the standard doses of antibiotics while only 7.7% had the dosage determined from body weight. None of the patients had serum levels of the antibiotics determined.

4.5.2 Antibiotics used for VAP Treatment

Table 10: **Antibiotic regimen used for VAP treatment**

Antibiotic regimen used for VAP treatment	Frequency	Percent
Ceftriaxone	8	20.5
Meropenem	6	15.4
Ceftazidime	2	5.1
Cefuroxime	2	5.1
Amikacin + Ceftriaxone	2	5.1
Coamoxiclav + Metronidazole	2	5.1
Meropenem + Metronidazole	2	5.1
Amikacin	1	2.6
Azithromycin	1	2.6
Coamoxiclav	1	2.6
Amikacin + Ceftazidime	1	2.6
Amikacin + Imipenem + Metronidazole	1	2.6
Ceftriaxone + Coamoxiclav	1	2.6
Ceftriaxone + Meropenem	1	2.6
Ceftriaxone + Meropenem + Amikacin	1	2.6
Ceftriaxone + Metronidazole	1	2.6
Ceftriaxone + Metronidazole + Coamoxiclav	1	2.6
Flucloxacillin + Metronidazole	1	2.6
Piperacillin + Tazobactam	1	2.6
Piperacillin + Tazobactam + Ceftriaxone	1	2.6
Imipenem	1	2.6
Imipenem/Cilastatin + Metronidazole	1	2.6
Total	**39**	**100.0**

Ceftriaxone monotherapy was the most commonly used (20.5%), followed by meropenem (15.4%). Ceftriaxone was also a major choice in combined therapy.

Table 11: Pharmacological classification of antibiotics used

Antibiotic classification	Antibiotic used	Frequency	Percent
Cephalosporins	Ceftriaxone	16	41.0
	Ceftazidime	3	7.7
	Cefuroxime	2	5.1
	Sub-total	**21**	**53.8**
Other beta-lactam antibiotics	Meropenem	10	25.7
	Imipenem	2	5.1
	Imipenem/Cilastatin	1	2.6
	Sub-total	**13**	**33.3**
Metronidazole	Metronidazole	9	23.1
Penicillinase resistant penicillins	Coamoxiclav	5	12.9
	Piperacillin + Tazobactam	2	5.1
	Flucloxacillin	1	2.6
	Sub-total	**8**	**20.6**
Aminoglycosides	Amikacin	6	15.4
Macrolides	Azithromycin	1	2.6

Cephalosporins formed the bulk of antibiotics (53.8%) used and in that class ceftriaxone was used in 41% of cases. In the class of other beta lactam antibiotics meropenem contributed to > 90% in that class.

4.5.3 Duration of VAP treatment with antibiotics

Twenty-eight (71.8%) of the patients sampled underwent five days of VAP treatment while eight (20.5%) were treated for seven days. (Mean=5.46 ± 0.37days, min=3days, max=10days, range=7days, mode=5days, median=5days).

Table 12: **Cost of VAP treatment with antibiotics**

Cost of VAP treatment (Ksh.)	Frequency	Percent	Cumulative Percent
< 5,000	15	38.5	38.5
5,000 - 10,000	6	15.4	53.8
11,000 - 20,000	1	2.6	56.4
21,000 - 40,000	5	12.8	69.2
41,000 - 80,000	8	20.5	89.7
81,000 - 160,000	4	10.3	100.0
Total	**39**	**100.0**	

A big proportion of the patients sampled (38.5%) used less than Kshs. 5,000 in the treatment of VAP, while on the higher side, (10.3%) spent Kshs. 81,000 – 160,000. (Mean=Kshs. 30,242.95 ± 11,097.34, min=Kshs. 1,125, max=Kshs. 135,000, range=Kshs. 133,875, mode=Kshs. 3,250, median=Kshs. 9,240).

4.6 RELATIONSHIPS

There was no significant relationship between the risk factors with onset of VAP (early or late onset).

There was no statistically significant relationship between the organisms isolated and onset of VAP in this study. This is probably because of small numbers in each group of organisms.

There was no relationship between onset of VAP (early or late onset) and the clinical outcome (death or discharge) observed. The statistics were generated excluding the patients still in ICU.

There was no relationship between drugs used and the clinical outcome (death or discharge) observed. The statistics were generated excluding the patients still in ICU.

There is a relationship between witnessed aspiration as a risk factor and isolated organisms.

5.0 DISCUSSION

Demographics and incidence

Three hundred and twenty patients were admitted to the ICU for the period from 1st April to 31st July 2009. One hundred and thirty nine of these were mechanically ventilated for ≥ 48 hours. Thirty-nine patients were diagnosed with Ventilator Associated Pneumonia (VAP) during the study period.

The incidence of VAP was 12.2% in this ICU population, and 28% of the mechanically ventilated patients. This agrees with previous studies which show that VAP affects about eight to 20% of ICU patients and up to 27% of MV patients.[3,5,8]

Age distribution was bimodal, most patients were between 21 to 30 years old (23.1%) followed by those above 60 years (20.5%). There were more male (69.2%) than female patients (30.8%). Most of the patients were either unemployed (35.9%) or self employed (30.8%) while only 20% were in formal employment. These demographics relate to the fact that this is a public hospital and hence low socioeconomic patients form the majority of patients attended to. Some patients are brought in unconscious, mostly after road traffic accidents hence their demographics are not known. In this study this group constitutes 7.7%.

The mean number of days that patients stayed in the ICU was 22.3 ± 2.9 days, with majority staying less than 30 days. A third of the patients stayed less than 10 days, these were mainly trauma patients with severe head injury who succumbed to their injuries within a few days.

Trauma patients had the greatest incidence of VAP consistituting 43.6%, followed by medical patients and surgical respectively. This confirms that most of the patients admitted to this unit are from road traffic accidents and assault (see Table 2 and Figure 4). This finding was not unexpected since several studies show that trauma predisposes one to VAP. The high incidence is also due to the need for immediate and longer MV since most trauma patients are received unconscious and require emergency intubation. Emergency intubation has its risks including causing more trauma to the respiratory tract and technique challenges depending on patient's status.

The mortality rate in this study was at 46.2%, and was higher in trauma patients (10 out of 17 cases giving 58.8%) than medical (five out of 15 cases, 33.3%). It is however noteworthy that previous studies have not clearly demonstrated that pneumonia is indeed responsible for higher mortality rate of these patients.[8] The difficulty in establishing a firm diagnosis and severe underlying illnesses predispose patients in ICU to development of VAP and higher mortality rates, hence difficulty to determine survival if no VAP occurred. This is partly because it is difficult to match patients with and without VAP who have similar characteristics.

The commonest mode of intubation for patients who developed VAP was orotracheal (76.9%), while the rest were on tracheostomy at the time they developed pneumonia. All patients in this unit who require MV are put on orotracheal tube then may or may not be changed to tracheostomy depending on how long they are expected to be ventilated. This definitely explains the fact that all patients on tracheostomy at the time of VAP diagnosis had late onset disease. It was noted that in this setting nasotracheal intubation is not used. This is in line with current trends elsewhere as this form of intubation increases the risk for sinusitis and other infections.

Pathogenesis

The mean number of days patients were on MV before development of VAP was 8.7 ± 0.9 , median was seven days (number of cases tapers off as days increase). Twenty two (56.4%) patients presented with late onset VAP whereas the rest (43.6%) had early onset disease. There is no significant difference in onset, though it agrees with the ranges given in other studies.[12,23,24]

Diagnosis of VAP still remains controversial and most of the clinical criteria used are subjective with differing sensitivity and specificity.[8] The diagnosis was made using the conventional clinical criteria supplemented by the tracheal aspirate cultures. A minimum of three clinical criteria (fever $\geq$ 38.5° C, low body temperature $\leq$ 35° C, hypoxia, WBCs $< 4 \times 10^9$ / l or $> 11 \times 10^9$ /l) and increased purulent sputum were used. An attempt to get radiological data was made, however very few patients (10.3%) had chest x-rays done to diagnose VAP. Many patients with positive tracheal aspirate cultures but no clinical signs of infection were left out of the study as they were considered only colonised but not infected with the organism isolated.

The microorganisms responsible for VAP may differ according to the population of patients in the ICU, [8] the duration of hospital and /or ICU stay and the diagnostic methods used. High rates of infection due to gram negative bacteria have been documented. The results of this study are comparable to previous studies on the predominant organisms.[16,17,25,42,46,53] *Staphylococcus aureus* was the only gram positive bacteria among the top five organisms causing 12.8% of the cases and its occurrence concurs with several studies. [16,17, 20,24,25]

The commonest bacterial pathogens isolated on tracheal aspirates were *Klebsiella* (23.1%,), *Citrobacter* (12.8%), *Staphylococcus aureus* (12.8%), *Pseudomonas aeruginosa* (10.3%) and *Acinetobacter* (10.3%). A previous study in the same ICU by Ngumi in 2006 showed the predominant organisms as *Pseudomonas, Klebsiella, Staphylococcus aureus* among others.[20] This implies that the prevalence of the organisms has not changed much for the last few years.

The high rate of polymicrobial infection has been emphasised in recent studies [8] and in this study nine out of the 39 patients had tracheal isolates with two or more organisms. Among the polymicrobial results *Klebsiella* species and *Pseudomonas aeruginosa* were the main organisms isolated in combination with others. Considering both the single and polymicrobial growths, *Klebsiella* was leading with 14 cases, followed by *Pseudomonas* (10 cases) then *Citrobacter* with eight cases.

There were no reports on the MBCs (minimum bactericidal concentrations) and MICs (minimum inhibitory concentrations) in the tracheal aspirate reports. These would however have been more applicable if drug levels determinations were being done in this unit. However some results were indicated as heavy, moderate or light growth. Heavy growth was reported in 20% of the cases, and the main organisms specified as heavy in some isolates were *Pseudomonas* , *Staphylococcus* , *Acinetobacter* , *Citrobacter* and *Proteus* species. Five out of the eight cases with heavy growth caused late onset VAP.

The organisms responsible for early onset VAP were not so different from those responsible for late onset disease. There was no significant relationship between types of organisms and onset of

VAP. It is however noteworthy that the potentially multidrug resistant organisms were responsible for both early and late onset of the disease.

Underlying disease may predispose to infection with specific organisms. However in this study there was no significant relationship between diagnosis at admission and organism causing VAP.

Sensitivity profiles

Of the 14 cases of *Klebsiella* isolated, ten were sensitive to meropenem, a carbapenem used for MDR organisms. This organism was mainly resistant to cephalosporins and coamoxiclav. These findings therefore show that meropenem is a good choice for treating VAP caused by *Klebsiella* group in this population.

Pseudomonas aeruginosa, generally a multidrug resistant organism was found to be very sensitive to meropenem (nine out the ten isolates were sensitive). Meropenem is a well known antipseudomonal antibiotic. *Pseudomonas* was also sensitive to ceftazidime, aminoglycosides and piperacillin/tazobactam . Resistance was exhibited by most other antibiotics tested (see Table 9).

Citrobacter species showed considerable resistance to cephalosporins and penicillins. It was most sensitive to meropenem, seven out of eleven cases.

Each of the organisms isolated exhibited some sensitivity to meropenem, though to different extents (Table 8).

Generally, meropenem seemed to have a broad cover especially for the MDR gram negative organisms such as *Pseudomonas, Klebsiella* and *Citrobacter.*

Risk factors

Risk factors for development of VAP can either be fixed which include neurological disease, trauma of head or thorax, chronic pulmonary disease, low GCS, burns, ARDS and sepsis among others or modifiable including witnessed aspiration, reintubation, paralysing agents, recent MV and enteral feeds.

From this study, modifiable factors were most common, with enteral feeds topping the list (Table 4). Almost all mechanically ventilated patients are put on enteral feeds for nutritional support apart from those who have an indication for parenteral feeds. A nasogastric tube is used to provide nutritional support as well as to evacuate gastric secretions. Though not directly a potential risk factor for VAP, this tube may increase oropharyngeal colonisation, cause stagnation of oropharyngeal secretions and increase risk of aspiration and reflux. Paralysing agents are next on list since most patients on MV are paralysed only at time of intubation while some may require paralysis for longer periods while in the ICU.

Reintubation after either accidental extubation or poorly planned extubation has been identified as a risk factor for VAP. It may cause injury to the already inflamed respiratory system as the tube is inserted, or reintroduce organisms colonizing the oropharyngeal and upper respiratory system lower down. During reintubation there may be direct aspiration of gastric contents into the lower airways particularly when a nasogastric tube is kept in place after extubation. Some of these are modifiable risk factors hence the importance of preventive measures is emphasized.

Treatment patterns

The diversity of microbial causes of VAP complicates selection of antibiotic therapy for VAP. Appropriate and adequate antibiotic therapy is necessary to reduce mortality due to VAP.[33 - 41] Knowledge of the sensitivity patterns in one's setting is crucial to ensure proper choice of drugs. Empiric treatment is important to ensure early and broad spectrum cover for the likely organisms. This aspect was not very clear in the setting of this study, since though some patients are started on antibiotics early in their stay in ICU, it may not necessarily be due to suspicion of VAP but rather to cover for infection in general. For such patients the antibiotic may be changed after culture and sensitivity results or due to clinical state of the patient not improving. For other patients, antibiotics were started after the culture results hence no empiric treatment was applied. Most clinicians just treated infection (basing decision on culture results and clinical status of the patient, not necessarily labelling it VAP).

The antibiotic dosage designs used were examined, for most patients the standard doses of the drugs were considered (61%) and choice of antibiotic mainly tied to the culture results. For the rest of the cases the clinician's judgement prevailed. Only for three patients (7%) was body weight used to calculate the drug dosage and this was solely for paediatric patients. No determination of antibiotic serum levels was done, even for the aminoglycosides where this is indicated. This may partly be due to unavailability of equipment for therapeutic drug monitoring.

Antibiotics for treatment of VAP may be used as single agents or in combination therapy. The frequencies of the different regimen used in this study are as shown in table 10. Single agents

were used in 22 out of the 39 patients studied. The other 17 patients were treated with combination of either two or three different antibiotics. In some cases the drugs were used sequentially rather than concurrently. It was observed that combination therapy were used in cases of MDR pathogens such as *Pseudomonas* and *Klebsiella*, in mixed or polymicrobial growth or just to broaden the cover for other organisms.

The most commonly used class of antibiotics was cephalosporins (53.8%) and the main drug in this class was ceftriaxone (41%). Overall ceftriaxone was the most commonly used antibiotic regardless of most organisms exhibiting resistance to it (Table 9). This may be explained by the observation that most patients were empirically put on this drug prior to culture and sensitivity results, after which the drug was either changed or retained.

Meropenem was the second most used for VAP treatment in this unit. It was used in cases of *Pseudomonas*, *Klebsiella* and *Citrobacter* groups and this agrees with the sensitivity patterns of these organisms (Table 8). Metronidazole was the next in number, used in nine cases. It was mainly used in combination with penicillins, cephalosporins and even aminoglycosides in a few cases, to give anaerobic cover. It actually did not feature in the sensitivity profiles.

The optimal duration of therapy remains unknown. Several studies have evaluated treatment courses ranging from three days to several weeks, based on the clinical response.[44 - 47] Usually, the aim is to reduce the exposure to antibiotics and avoid resistance development. Previous studies show no difference between eight and 15 days of therapy.[15,19] The duration of therapy used for most patients in this study was five days (71.8%) followed by seven days.

There was no particular relationship between the length of treatment and the organism isolated, most clinicians start with the conventional five or seven days and adjust duration according to the patient's response.

The cost of treatment was dependent on the drug chosen to treat, this of course related also to the organism isolated and its sensitivity profile. Majority of patients (38.5%) used less than khs. 5000. This clearly correlates with the high usage of ceftriaxone which costs about ksh 1125 for a five-day course of the antibiotic. On the higher side of drug costs we had 30.5% of patients who spent more than ksh 40,000. Contributing to this high cost was mainly meropenem which is a choice for most resistant pathogens, imipenem and piperacillin/tazobactam. This may be justified by the fact that most patients on these drugs survived and were discharged from the ICU. This may however not be the sole reason since many other factors determine patients outcome in ICU setting. This cost challenge on the other hand is eye opening in that more stringent measures are required to prevent VAP in ventilated patients.

6.0 CONCLUSION

The incidence and pathogenesis of VAP at the Kenyatta National Hospital ICU compares with other studies done elsewhere. This unit admits a high percentage of trauma patients hence need to be on the look out for VAP as trauma predisposes patients to this disease.

The common pathogens and their sensitivity profiles are determined and match with a previous study. The antipseudomonal antibiotics used here are found to be effective. Meropenem, though an expensive drug compared to others is the best choice for infections caused by *Pseudomonas* and *Citrobacter* species in this unit.

Most of the documented risk factors for VAP in earlier studies were identified in this study. The commonest modifiable risk factors were enteral feeds and use of paralytic agents, both of which are important in the care of critically ill patients.

RECOMMENDATIONS

Future work in this area would involve:

- A further study involving a larger population is proposed to better document these findings.
- The KNH ICU team should be advised to identify patients who have modifiable risk factors early enough, to better their management.
- A more comprehensive antibiotic use review should be conducted in order to develop a formulary for treatment of VAP in the institution.
- Studies to assess the preventive measures for VAP and check on their effectiveness in reducing prevalence of VAP.
- Studies to assess how VAP affects length of stay in ICU and effect on cost of health care as compared to other illnesses.

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8.0 APPENDICES

8.1 APPENDIX 1

DATA COLLECTION FORM

Study number: ..... Date: .....

A. PATIENT BIODATA

Age: ..... Gender:..... Weight .....
Married [ ] Single [ ] Divorced [ ] Widowed [ ]
Occupation .....
Level of education
Elementary [ ] Secondary [ ] College [ ] University [ ]

B. HOSPITALIZATION

i. Admission details

Date of Admission to hospital:..... Date of Admission to ICU:.....

Date of Discharge/ death: ..... Length of ICU stay: .....

ii. Mechanical ventilation

Date of intubation: ..... Date of extubation: .....

Tube used: (tick as appropriate)
Nasotracheal[ ] Orotracheal[ ] Tracheostomy [ ]

Naso/orotracheal then tracheostomy [ ]

iii. Diagnosis at admission to ICU:

Category :(Tick as appropriate)
Medical [ ]
Surgical [ ]
Trauma [ ]
Other: (specify) .....

Primary diagnosis.....

Secondary diagnosis.....

C. RISK FACTORS CONTRIBUTING TO DEVELOPMENT OF VAP IDENTIFIED IN THE PATIENT AT ADMISSION OR DURING THE ICU STAY: (Tick as appropriate)

ARDS	[ ]	Burns	[ ]	Chronic pulmonary disease	[ ]
Enteral feeds	[ ]	Neurological disease	[ ]	Paralytic agents	[ ]
Recent MV	[ ]	Sepsis	[ ]	Trauma (thoracic/head)	[ ]
Witnessed aspiration	[ ]	Low GCS	[ ]	Reintubation	[ ]

D. DIAGNOSIS OF VAP

i. After how long on mechanical ventilation was diagnosis made? .....
Depending on number of days on MV at time of diagnosis, classify as either:

Early onset VAP [ ] or Late onset VAP [ ]

ii. Clinical criteria

Fever Yes [ ] No [ ] New purulent sputum Yes [ ] No[ ]

Low body temperature Yes [ ] No [ ] Hypoxia Yes [ ] No[ ]

WBC > 10,000/mm^3 or < 4,000/ mm^3 Yes [ ] No [ ]

iii. Radiological criteria

New or enlarging infiltrate on chest x-ray Yes[ ] No[ ]

iv. Microscopic culture and sensitivity: Tracheal aspirate

Organism isolated. Antibiotics Sensitive to Antibiotics resistant to

MICs available Yes [ ] No [ ] MBCs available Yes [ ] No [ ]

E. TREATMENT OF VAP

Design of dosages of antibiotics

Used standard dosing of drugs Yes [ ] No [ ]
Used body weight Yes [ ] No [ ]
Used drug levels determination Yes [ ] No [ ]

Drugs used for VAP treatment

Drug	dose	route	frequency	duration	cost of regimen
1.					
2.					
3.					

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8th April 2009

Rosaline Njoki Kinuthia
Dept. of Pharmaceutics & Pharmacy Practice
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Dear Rosaline

Research proposal: "Determination of the Risk Factors and treatment patterns of Ventilator Associated Pneumonia in Intensive Care patients at Kenyatta National Hospital" (P27/2/2009)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your above revised research proposal for the period 8th April 2009 –7th April 2010.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF. A N GUANTAI
SECRETARY, KNH/UON-ERC

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