PREVALENCE AND INCIDENCE OF INFECTIONS AND SEPSIS IN CRITICAL CARE UNITS AT TWO TERTIARY REFERRAL HOSPITALS IN KENYA

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TABLE OF CONTENTS

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LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABSES	Abdominal Sepsis Study
BSI	Bloodstream Infections
CAP	Community-acquired Pneumonia
CAUTI	Catheter-Associated Urinary Tract Infection
CCU	Critical Care Unit
CLABSI	Catheter Line Associated Bloodstream Infections
CNS	Central Nervous System
CRI	Catheter-Related Infections
CSF	Cerebrospinal Fluid
DIC-	Disseminated Intravascular Coagulation
EPIC	Extended Prevalence of Infection in Intensive Care
ESBL	Extended Spectrum Beta Lactamase
GCS	Glasgow Coma Scale
GDP	Gross Domestic Product
HAP	Hospital-acquired pneumonia
HCAP	Health-Care-Associated pneumonia
HDU	High Dependency Unit
HIV	Human Immunodeficiency Virus
ICON	Intensive Care Over Nations audit
ICP	Intracranial Pressure
ICU	Intensive Care Unit
ISF	International Sepsis Forum
KNH	Kenyatta National Hospital
LODS	Logistic Organ Dysfunction Score
MDRO	Multi-Drug Resistant Microorganisms
MICU	Medical-Intensive Care Unit
MRI	Magnetic Resonance Imaging
MTB	Mycobacterium Tuberculosis Bacteria
NNIS	National nosocomial infection surveillance system
PCR	Polymerase Chain Reaction
SAS	Subarachnoid Space
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment Score

TB	Tuberculosis
TBM	Tuberculous Meningitis
TNF	Tumor Necrosis Factor
KNH/UON-ERC	Kenyatta National Hospital /University of Nairobi Ethics and Research Committee
UTI	Urinary Tract Infection
USD	United States Dollar
VAP	Ventilator-Associated Pneumonia

ABSTRACT

Background: Sepsis is a major global challenge affecting millions of individuals yearly. The incidence of sepsis has been estimated to be 535 per 100000 person-years however, this varies by geographical region. In Critical care units, sepsis accounts for 29% of Critical care unit (CCU) admissions with an estimated mortality of 25%. common causes of sepsis are respiratory tract infections, intra-abdominal infections, urosepsis, and catheter-related bloodstream infections. Nosocomial infections are frequent causes of sepsis in Intensive Care Units, with patients having a 2-5 times increased risk of developing nosocomial infections as compared to the general hospital population. The prevalence of multi-drug resistant infections is also significantly higher with Multidrug-Resistant Organisms (MDROs) such as Pseudomonas and Acinetobacter being responsible for a large portion of nosocomial infections.

Objectives: To determine three-month period prevalence and incidence rates of infections, sepsis and septic shock in adult patients admitted to CCU's at tertiary care hospitals in Nairobi. We aimed to document primary infection foci,causative organisms, and their antibiotic susceptibility patterns. We also aimed to determine the 28-day case fatality rates in patients with infections, sepsis, and septic shock.

Study Design: This was a hospital-based prospective observational study among patients admitted to the adult Critical Care Units at the Kenyatta National Hospital and the M.P Shah Hospital carried out between December 2020 and March 2021

Study Site and Subjects: The Kenyatta National Hospital (KNH) is a national tertiary referral hospital with an 1800 bed capacity, medical Critical Care Units (CCU's)with six beds each as well as a multidisciplinary CCU with 20 beds. The M.P. Shah Hospital is a 200-bed private tertiary level facility with a 16 bed CCU. All consecutive patients admitted to these adult CCU's meeting the inclusion criteria were eligible to participate in the study.

Methods: All patients admitted to the Critical Care Units were evaluated on admission using the International Sepsis Forum (ISF) Consensus definitions for presence of infection(s). The Sequential Organ Failure Assessment (SOFA) score was applied to all patients to identify those with sepsis. A patient case report form was used to collect data and patients were followed up from admission to discharge from the CCU. Patients were assessed at intervals for development of incident infections, sepsis and septic shock. Microbiologic culture reports were also documented to determine isolates and antibiotic susceptibility patterns. Vital status for all

subjects at 28 days was assessed via either direct follow up for non-discharged patients and via telephone contact for patients who had been discharged. The primary investigator and research assistants were not involved in patient care or management.

Statistical Analysis: Proportions and 95% confidence intervals were calculated as the number with the event of interest (infection, sepsis) divided by the total sample size. Case fatality rates were calculated for the CCU's as well as for patients with sepsis and septic shock. The analysis was done for the combined sample size and further stratified by hospitals (KNH and MP Shah). Prevalence, incidence and mortality rates for KNH and MP Shah were compared using a chi-squared test.

Results: A total 160 subjects were recruited (108 from KNH and 52 from MPSH. The prevalence of infection, sepsis and septic shock on admission were 52.5% (95% CI: 44.5-60.4), 35% (95% CI: 27.63-42.93) and 13.8% (95% CI 8.82-20.07) respectively. The incidence of infections, sepsis and septic shock were 41.3% (95% CI: 33.5-49.3), 31.8% (95% CI: 20.9-44.4) and 27.2% (95% CI: 17.0-39.6). The 28-day case fatality rate (CFR) for the sample cohort was 38.8% (95% CI: 31.2-46.8). Among patients with sepsis and septic shock, the CFRs were 46.8% (95% CI: 35.3-58.5) and 59.1% (95% CI: 36.4-79.3) respectively. Foci of prevalent infection were mainly respiratory and intra-abdominal while foci of incident infection were mainly Catheter associated urinary tract infections and ventilator associated pneumonia. The most common organisms isolated were Gram-negative bacilli.

Conclusion: Our study demonstrated high prevalence rates and incidence rates of infections, sepsis and septic shock among critical care patients at KNH and MPSH with higher-than-average case fatality rates in all sample cohorts. Incident infections were primarily related to invasive devices such as urinary catheters, endotracheal tubes and intravascular catheters.

1.0 BACKGROUND

Sepsis is defined as a "syndrome of physiologic, biologic and pathologic abnormalities induced by infection"(1) In the critical care population, sepsis accounts for more than a quarter of all admissions and is associated with an increase in mortality rates (2). There is increasing data that demonstrates that patients who have suffered from sepsis develop significant long term complications(3). Although several studies have provided epidemiological data on sepsis in high income countries, there is a sizeable deficit of data regarding the burden of sepsis in lower income countries and Sub Saharan Africa (4) .

Sepsis accounts for 29.5% of all diagnoses amongst critical patients worldwide (2). The general prevalence rate of sepsis is estimated at 535 cases per 100,000 person-years with an analysis of 27 studies illustrating more than 30 million incident cases of sepsis and more than 19 million incident cases of severe sepsis occur worldwide (5) .

Patients with sepsis have an elevated mortality rate of 25% as compared to 16% for patients in the Intensive Care Unit (ICU) admitted without sepsis (2). These numbers vary according to geographical region with mortality rates in the United States at 19% as compared to 27% in Uganda (6), (7).

This has been attributed to differences in populations, availability of care, and aetiogenesis. The ICON audit showed that ICU patients from low-income countries had a higher mortality as compared to upper- and middle-income countries. Currently, there is limited epidemiological data on sepsis in developing countries where the prevalence and incidence rates are higher.

Septic shock is a more severe subset of sepsis in which profound metabolic abnormalities result in cardiovascular instability. Septic shock carries a mortality rate of approximately 60%.

Hospital-acquired infections contribute significantly to mortality and morbidity and are a significant cause of sepsis in ICU patients. Critical care units suffer from an increased burden of nosocomial infections that is 2-5 times higher than general inpatient populations as critically ill patients are commonly immunosuppressed and often require invasive procedures. (8).

The INDICAPS study demonstrated an incidence of infections in the ICU of 12.2% with a mortality of 28% (9). A point prevalence study done in multiple Intensive care units (ICU) in Turkey showed that 57% of ICU patients had infections. Out of these, 54% were nosocomial infections (10).

Multidrug-resistant organisms pose an emergent problem in-hospital care. A study in 2006 at the KNH, ICU isolated *Pseudomonas aeruginosa*, *Klebsiella*, *Citrobacter*, *Staphylococcus Aureus, and Streptococcus Pneumoniae* as common pathogens. (11) A similar surveillance study in South Africa in 2018 isolated *Klebsiella Pneumoniae* as the most common cause of healthcare-associated infections with over half of the isolated bacteria demonstrating resistance to penicillin(12). Additionally, 74.8% of Acinetobacter species, 39.0% of Klebsiella species and 26.5% of Pseudomonas species isolates were resistant to carbapanem antibiotics (10). Additionally, a surveillance study in Kenya published a Methicillin Resistant Staphylococcus Aureus (MRSA) prevalence of 54% at Kenyatta National Hospital (13).

Data regarding the prevalence and incidence of sepsis as well as the types of infections, pathogens isolated, and antibiotic susceptibility patterns would be invaluable in quantifying the burden of sepsis in Intensive care units while knowledge of causative organisms and local antibiotic susceptibility patterns is essential in guiding antibiotic selection and empiric treatment.

2.0 LITERATURE REVIEW

2.1 The Burden of Sepsis

As of 2017, the incidence of sepsis worldwide was more than 48 million cases. Furthermore there were over 11 million sepsis-related mortalities (14). In the United States of America (USA) sepsis is the commonest cause of in-hospital mortality and has a financial burden of more than 24 billion United States Dollars (USD) annually (14).

The average global prevalence of sepsis in ICU on admission is approximately 18%. Total prevalence rates at 28 days post admission are approximately 29%. Incidence rates of sepsis in ICU patients was 11% according to a recent multi-center audit (2).

Septic shock which is a more severe subset of sepsis, has a prevalence of 16% in ICU patients at 28 days.

In Africa, morbidity and mortality from sepsis is estimated to be even higher given the lack of resources and an increased burden of Human Immunodeficiency Virus (HIV) and related illnesses. (15). A recent audit demonstrated increased morbidity and mortality from sepsis in countries with a lower Gross Domestic Product (GDP) (2). ICU mortality rates from sepsis in Africa were as high as 35% compared to 25% in developed countries. Septic shock has an even higher mortality of greater than 40% (16). In Kenya, there is limited epidemiological data on the burden of sepsis with regards to incidence, prevalence and mortality rates. Quantifying the burden of sepsis in Sub-Saharan Africa is challenging because most of the data has been obtained from studies in high income countries. The African ICU population has also been grossly under-represented in most international studies (2).

2.2 Definitions of Sepsis

Over recent years, the definitions of sepsis and septic shock have evolved considerably. The third international consensus of definitions for sepsis are universally accepted. Previously the view held that sepsis resulted from a systemic host inflammatory response syndrome to infection, Systemic Inflammatory Response Syndrome (SIRS). Severe sepsis which was a progression of the disease process occurred when organ dysfunction developed due to sepsis. The addition of cardiovascular instability defined “septic shock” (16).

As per the current guidelines, sepsis is defined as “a life-threatening organ dysfunction caused by a dysregulated host response to infection” (16). Organ dysfunction in patients with infection is identified through use of the SOFA score based on an increase in the SOFA score by two or more points. (16)

Septic shock is defined as “a subset of sepsis in which marked circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality as compared to sepsis” (16).

Identification of septic shock requires the presence of cardiovascular instability which is evidenced by a mean arterial pressure less than 65mmHg necessitating the use of vasopressors and blood lactate levels above 2mmol/L despite adequate fluid resuscitation (16).

The use of lactate remains controversial however it is included in the definitions to identify patients with a higher mortality risk. In settings in which lactate measurements are unavailable, a working diagnosis of septic shock using hypotension and other clinical indices of tissue hypoperfusion (e.g., delayed capillary refill) may be an equivalent substitute, however, this is not as objective. Identification of patients with septic shock is of limited clinical value rather than epidemiological, since patient management is likely to remain unaltered (16).

2.3 Pathogenesis of Sepsis

Sepsis results from a complex and dysregulated immunological response to infection. Untreated, sepsis progresses to hypoperfusion, hypoxia, and profound cellular dysfunction which manifests in tissues, organs and organ systems, leading to a mortality rate of at least 30%. The clinical syndrome of sepsis is a manifestation of excess inflammation and inflammatory cytokines that lead to disruptions in coagulation causing micro-thrombi and impediment of microcirculatory flow leading to multi-organ failure (17).

Dysregulated Coagulation

The coagulation cascade is a complex interplay of pro and anticoagulant factors. In sepsis, excess inflammation leads to significant disruptions within both the coagulation pathways and its regulatory system. Septic patients develop severe coagulopathy with severe depletion of platelets and clotting factors accompanied by microvascular thrombus formation. This leads to alteration of laminar blood flow, occlusion of blood vessels, and eventual tissue hypoperfusion with further cell injury and tissue hypoxia (18).

Hyper-inflammatory Response

The hallmark of sepsis is a hyperactive immune response that results in gross physiological abnormalities that lead to generalized inflammation in all organ systems (18). This is based on evidence that shows septic patients have increased levels of cytokines such as Tumor Necrosis Factor (TNF) and were found to have an increased mortality (19). The classic endotoxic model of sepsis was created after the discovery that injection of large doses of endotoxin produced a massive systemic inflammatory response (20).

Cellular Dysfunction

Cellular dysfunction is characterized as either excessive or depressed metabolic function. Excessive activation refers to a hyperreactive cellular response to stimuli, for example, an exaggerated neutrophil response with formation of toxic products that cause cellular injury. An example of a depressed function would be a failure of lymphocytes phagocytosis. Lymphocytes are crucial to the clearance of infectious pathogens. However, septic patients suffer from exaggerated lymphocyte apoptosis which leads to reduced lymphocyte function (21). Endothelial cell dysfunction occurs in sepsis due to endothelial cell injury as well as the release of histamine, serotonin, and endothelial nitric oxide that directly affects the capillary endothelium (22).

Metabolic Derangements

A state of hypermetabolism in sepsis leads to consumption of resources such as glutathione, increased oxygen demands and excessive lactate formation. Glutathione is responsible for neutralizing hydrogen peroxide which an oxidative agent that is produced during normal metabolism. Lack of glutathione leads formation of excess hydrogen peroxide which causes severe oxidative injury to cells and organs. Glutathione depletion occurs in sepsis and septic shock which worsens the pathology eventually resulting in a worsening cellular damage (23). Lactate synthesis increases when pyruvate formation increases in a septic state. The excess pyruvate is then converted to lactate in the cytoplasm by lactate dehydrogenase resulting in lactic acidosis (23).

Progression to Septic Shock

The progression of sepsis to septic shock is due to a culmination of the above cellular and metabolic factors. Firstly, the massive cytokine release leads to systemic vasodilation with pooling of blood in the peripheral circulation. Loss of systemic vascular resistance leads to hypotension and hypoperfusion of vital organs. Buildup of lactic acid leads to a metabolic acidosis with resulting myocardial depression and worsening hypotension. Eventually, circulatory collapse ensues with significant end organ damage (23).

2.4 Sequential Organ Failure Assessment Score (SOFA)

The presence and severity of organ dysfunction in ICU patients can be identified through use of the SOFA score. It is based on a composite of six different scores, one for each major system: Pulmonary, cardiovascular, hepatic, coagulation, renal and neurological. Each criterion is scored from 0 to 4. An increasing score reflects worsening organ failure for each system (24). Specific parameters measured in the SOFA score are as follows:

- Pa02/Fi02
- Glasgow Coma Scale
- Mean arterial Pressure with and without inotrope use
- Serum Bilirubin level
- Thrombocyte count
- Serum creatinine level and urine output

According to guidelines, sepsis can be identified as an immediate change in the SOFA score by 2 or more points in patients with infection. Patients without pre-existing organ failure are assigned a baseline score of zero (25).

The SOFA score is widely used because an increasing SOFA score is an accurate predictor of mortality in septic patients. An increase of 2 or more points in the SOFA score correlates with a mortality risk of 10% in patients with infection (16) (26).

Other scoring systems that have been compared with the SOFA are the Logistic Organ Dysfunction System (LODS), however, due to its accuracy and simplicity, the SOFA score has been advocated for use in the current sepsis guidelines (16).

2.5 ICU Acquired Infections

Infections in the ICU can either be classified as either community acquired or nosocomial.

A nosocomial infection is defined as "an infection that is not present or incubating when the patient is admitted to a hospital" (27). The burden of nosocomial infections in the ICU is significantly elevated with incidence rates more than double as compared to the general hospital population (28).

The incidence of ICU acquired infections varies from region to region based on demographic differences and patient characteristics. A large international study done in 8 countries reported an incidence of infections in ICU of 21% at admission and 18% within 24 hours after admission (29). In the Extended Prevalence of Infection in Intensive Care (EPIC) study involving more than 1000 ICU s from over 75 countries, 51% of patients had nosocomial infections. The most

common infections were respiratory 64%, followed by intra-abdominal 19% and bloodstream 15% (30).

Critical patients are also at risk for multiple infections due to the presence of risk factors such as multiple invasive devices. The probability of developing a second infection has been found to be 11 times higher after a first infection has occurred. Multiple infections have also been associated with a prolonged hospital stay. (31)

2.5.1 Respiratory Tract Infections

Respiratory infections are the commonest nosocomial complications in ICU's and the commonest cause of sepsis (30). 60% of all infections in ICU are respiratory in origin according to data from the EPIC study. Respiratory infections can either be:

i. Community-acquired Pneumonia (CAP)

ii. Hospital-acquired pneumonia (HAP) which includes:

- ICU acquired pneumonia which comprises of:
  - Ventilator-associated pneumonia
  - Non- Ventilator associated pneumonia

CAP is defined as pneumonia that was not acquired during hospital stay or in contact with a healthcare facility (32).

The range of causative microorganisms isolated in patients with CAP varies between studies and depends on the patient population studied. Common causes of CAP include *Streptococcus pneumoniae, Haemophilus influenza, Staphylococcus aureus, Pseudomonas aeruginosa , Klebsiella pneumoniae* and other respiratory viruses(33) .However, a study done in Sudan, showed *P. Aerueginosa and K. Pnemoniae* as the commonest isolates in patients with CAP which were sensitive mainly to Carbapenems (34). A study in Nigeria isolated Klebsiella Pneumoniae as the commonest community acquired pathogen in patients with pneumonia which was sensitive to Levofloxacin and Ceftazidime but resistant to Amoxicillin-clavulinic as well as Ceftriaxone.

Hospital-acquired pneumonia (HAP), or nosocomial pneumonia, is defined as "a lower respiratory infection that was not incubating at the time of hospital admission and develops clinically two or more days after hospitalization". If this occurs in the ICU, it is termed as ICU acquired pneumonia. Causative micro-organisms associated with ICU acquired pneumonia include Gram negative bacilli such as *Pseudomonas aureginosa,, Klebsiella Pneumonia,*

Acinetobacter. (32). Antibiotic resistance exhibited by pathogens is common with most isolates resistant to third generation cephalosporins. Sensitivity varies with high levels of susceptibility towards piperacillin-tazobactam and carbapanems (35).

Ventilator Associated Pneumonia (VAP) is defined as "pneumonia that develops more than 48 hours after endotracheal intubation and mechanical ventilation" (32). Ventilator associated pneumonia accounts for 86% of nosocomial pneumonias with an incidence of approximately 5-10% per 1000 hospital admissions. The mortality attributed to VAP is variable ranging from 0-50% depending on the patient populations (36).

Ventilator-associated pneumonia is identified by development of a new infiltrates on chest radiograph with accompanying leukocytosis, and purulent tracheobronchial secretions. The common organisms associated with VAP are depicted in table 1. Antibiotic susceptibility patterns are similar to nosocomial pneumonia with high levels of multi-drug resistance and ESBL producing pathogens.

***Table 1:Causative organisms of ventilator associated pneumonia*(37).**

MDR: Multi drug resistant. Spp: species

Non- MDR Pathogens	**MDR Pathogens**
Streptococcus pneumoniae	*Pseudomonas aeruginosa*
Hemophilus influenzae	Methicillin resistant S. aureus
Methicillin Sensitive *S. Aureus*	*Acietobacter spp.*
Sensitive Enterobacteriaceae: *E.Coli, K. Pneumoniae, Enterobacter spp*	ESBL positive Enterobacteriaceae
	Legionella pneumophilia
	Aspergillus

2.5.2 Infections of the Central Nervous System (CNS)

Infections of the CNS are a significant cause of admission to the intensive care unit (ICU). CNS infections account for approximately 19% of infections seen in ICU according to a study done in Turkey (10). Diagnosis is challenging due to the lack of sensitive diagnostic tests (38). Geographically the burden of CNS infections is highest in low- and middle-income countries. CNS infections are associated with a high mortality rate, In Africa, the 1-year mortality was 49% for pneumococcal meningitis (39)(40).

The Major CNS Infections Are**:**

Meningitis: This is defined as "an acute purulent infection within the Subarachnoid Space (SAS)." It results in severe meningeal inflammation that leads to decreased levels of consciousness, ischemic cerebral infarcts, convulsions and raised Intracranial Pressure (ICP). The meninges, SAS, and brain parenchyma may all be simultaneously involved leading to meningo-encephalitis (41). Eliciting the diagnosis is based on recognizing a combination of clinical signs, symptomatology, cerebrospinal fluid biochemistry as well as microscopy, culture, and sensitivity (41). The incidence of bacterial meningitis in sub-Saharan Africa is 65 per 100000 cases which is greater than the average incidence in the USA (2.5/100000 cases). (42) .

Tuberculous Meningitis (TBM) is a severe manifestation of Mycobacterium Tuberculosis Bacteria (MTB) infection which frequently results in admission to ICU due to complications such as hydrocephalus, brain infarction, tuberculomas, and basal arachnoiditis. Diagnosis is based on clinical symptoms and signs, isolation of Mycobacterium Tuberculosis bacilli in Cerebrospinal Fluid (CSF), high lymphocyte counts in CSF, elevated protein levels in CSF, Tuberculosis Polymerase Chain Reaction (TB PCR) studies, and suggestive Magnetic Resonance Imaging (MRI) findings(43).

Encephalitis: Acute encephalitis is defined as inflammation of the brain parenchyma associated with neurological dysfunction (44). Encephalitis is a severe neurologic disorder with approximately 50% of cases requiring ICU admission due to seizures, coma, or respiratory failure (45). Patients with encephalitis commonly present with fevers, altered levels of consciousness, and focal or generalized neurologic deficits. Causative organisms for bacterial encephalitis include Hemophilus influenzae, Neisseria meningitis, and Treponema pallidum. (37).

2.5.3 Urosepsis

Urosepsis is defined as sepsis syndrome arising from an infection of the genitourinary tract (46) . Urosepsis accounts for between 9-31% of cases of sepsis. The prevalence of urosepsis in the ICU was 7.8% in Turkey and 14% according to a multicentre international trial (30). Common pathogens isolated are E. coli (52%), *Proteus* species, *Enterobacter species, Klebsiella species* and *Pseudomonas Aureginosa*. *Enterococci* accounted for approximately 5% of isolates(46). Urosepsis can be classified into catheter and non-catheter associated urinary tract infection. Catheter-Associated Urinary Tract Infection (CAUTI) is the commonest

nosocomial infection accounting for 40% of cases. Up to 50% of patients with in dwelling catheters for >5 days will develop a urinary tract infection. Candida infections are also associated with Urinary Tract Infections (UTI's) more frequently seen in catheterized patients in the ICU. Diagnosis is based on both clinical and microbiologic evidence.

2.5.4 Intra-Abdominal Infections

Abdominal sepsis represents an inflammatory response to bacteria such as Gram-negative, Gram-positive, or anaerobes which lead to an inflammatory cascade that results in the sepsis syndrome. The range of intra-abdominal infections can range from solid organ infections such as the liver, gall bladder, and biliary tract to primary and secondary peritoneal infections. Intra-abdominal sepsis accounts for 20% of all infections seen in ICU patients and is the commonest surgical cause of sepsis in the ICU (30).

A multinational study found secondary peritonitis as the commonest intra-abdominal infection in ICU (68%) followed by biliary tract infections (12%) and intra-abdominal abscesses (6%) (47). The same study found Gram-negative bacteria as the commonest isolates with *Escherichia Coli* isolated as the commonest pathogen (36%). Fungi were isoalted in 13% of patients (47). Multi-drug resistant organisms were responsible for up to 26% of intra-abdominal infections with ESBL Gram-negative bacteria isolated in 16% of culture specimens and carbapenem resistant bacteria isolated in 7% of specimens (47) .

Patients with intra-abdominal sources of sepsis have significant morbidity and mortality. The "AbSeS" study demonstrated an overall mortality of 29% which increased directly with the patients SOFA score (47).

2.5.5 Skin and Skin Structure Related Infections

Skin and Soft Tissue Infections (SSTIs) are common and include a range of illnesses from cellulitis to necrotizing fasciitis. They can also result from a surgical wound and are hence termed surgical site infections (1). They account for approximately 3% of infections seen in ICU patients and cause 4% of the cases of sepsis in ICU (10). In Africa, the prevalence is higher with skin infections accounting for 9% of infections in ICU. In a study done in Portugal, the commonest skin infections seen in ICUs were necrotizing fasciitis, skin abscesses, and cellulitis. In the same study, out of all patients admitted to ICU with skin infections, 70% were community-acquired while 30% were hospital-acquired (48).

In a Taiwanese study, the commonest SSTI's that were seen in ICU patients were cellulitis, decubitus ulcers, and surgical site infections which altogether accounted for 72% of skin infections in the ICU. A further 24% of skin infections in the ICU were caused by necrotizing fasciitis, vascular implants/devices, and gangrene (49). The commonest micro-organism isolated was E. coli in patients with necrotizing fasciitis. *Streptococcus Pyogenes* was isolated commonly from abscesses. Multi-drug resistant bacteria were isolated from 7% of specimens (48).

2.5.6 Intravascular Catheter Related Sepsis

Catheter Line Associated Bloodstream Infection (CLABSI) is defined as "the presence of bacteremia originating from an intravenous catheter"(1). Based on global surveillance data, the incidence of CRBSI was 2.1 per 1000 catheter days for respiratory ICU's, 5.1 for medical-surgical ICUs and , 30.2 for burn units (50).

The EPIC study demonstrated that 4.5% of all infections seen in ICU patients in Africa were catheter-related (30).

Clinical suspicion of Catheter-Related Infections (CRI) is high in patients with unexplained bacteremia and an indwelling catheter for more than 7 days while confirmatory diagnosis is based on positive catheter tip cultures alongside positive blood cultures for the same organism. Research done in India in 2011 showed 36% of the pathogens causing CRI's were Gram-negative and 64% were Gram-positive. Causative organisms responsible for causing CRI were *Staphylococcus aureus* (40%), *Pseudomonas aeruginosa* (16%), and *Klebsiella pneumoniae* (8%) (51).

2.5.7 Bloodstream Infections

Bloodstream infections (BSI) account for 40% of cases of sepsis in ICU. This may be underestimated as patients frequently receive broad-spectrum antibiotics before blood culture samples have been drawn. Currently, BSIs are classified into two groups: (16)

- Primary BSI comprising of BSIs of unknown origin in patients without an identifiable focus of infection
- Secondary BSI due to a microorganism related to an infection at another site

According to international definitions, BSIs also include Infective endocarditis based on the Duke's diagnostic criteria. (1) Infective endocarditis accounts for 1% of ICU admissions and has a mortality of 33%. (1)

For community-acquired infections, causative organisms isolated were mainly *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Escherichia coli* (52).

For nosocomial and Health-Care-Associated (HCA) bloodstream infections, antimicrobial susceptibility patterns depend on local epidemiological data. The incidence and prevalence of multi-resistant drug microorganisms is increased in patients with nosocomial blood stream infections with organisms such as Methicillin resistant *Staphylococcus Aureus,* Extended Spectrum Beta Lactamase *(*ESBL) producing *Enterobacteriaceae,* and *Pseudomonas aeruginosa* frequently isolated (52).

3.0 STUDY JUSTIFICATION

Patients diagnosed with sepsis in Critical Care Units (CCU's) suffer from a significantly elevated morbidity and mortality of up to 30%. Mortality rates from sepsis also vary between countries. There is a knowledge gap regarding the incidence, prevalence, and mortality rates of sepsis in CCU's in Kenya and Sub-Saharan Africa. Knowledge of local prevalence and incidence rates of infections and sepsis in the critical care population can enable quantification of the local burden of sepsis hence enabling prioritization of resources towards improving patient outcomes.

Data regarding case fatality rates from patients who have infections and sepsis can enable comparisons to be made with other countries globally. This will also lay the foundation for further research into sepsis with the aim of reducing mortality.

Nosocomial infections account for a large portion of infections treated CCU's and a significant cause of sepsis and mortality in this patient cohort. Knowledge of the primary infection sites, causative organisms and their antimicrobial resistance patterns can aid clinicians in the diagnosis of sepsis as well as target treatment towards the specific etiology.

4.0 RESEARCH QUESTION

What is the burden of infections and sepsis in Critical care units at tertiary care hospitals in Kenya?

5.0 OBJECTIVES

Broad Objective

To determine prevalence and incidence rates of infections and sepsis in adult patients admitted to Critical care units at the Kenyatta National Hospital and the M.P Shah Hospital, (Nairobi).

5.1 Primary Objectives

a) To determine the three-month period prevalence and incidence of infections in critical care patients.

b) To determine the three- month period prevalence and incidence of sepsis.

c) To determine the 28-day case fatality rate in patients with no infections, infections, and sepsis.

5.2 Secondary Objectives

a) To document causative organisms isolated from critical care patients with infections over a three-month data collection period.

b) To describe the foci of infection in critical care patients.

c) To describe antibiotic susceptibility patterns from organisms isolated in patients with infections.

d) To determine the three- month period prevalence and incidence of septic shock in critical care patients.

6.0 STUDY METHODOLOGY

6.1 Study Design

This was a prospective cohort observational study carried out over a total of four months between December 2020 and March 2021. Three months were used for patient recruitment with a 28 day follow up period to assess mortality.

6.2 Study Site

The study was carried out at two hospitals:

a) Kenyatta National Hospital: This is a national tertiary referral parastatal that is fee subsidized with a 1600 bed capacity. The multidisciplinary CCU (20 bed capacity) as well as two medical ICU's (10 bed capacity) was used in the study.

b) M.P. Shah Hospital: This is a private fee for service tertiary referral hospital with a 200-bed capacity and a 16-bed CCU. The selection of M.P Shah Hospital as a study site despite the comparatively lower bed capacity allowed for inclusion of a larger and more diverse study population from a private referral hospital as well as supplementing the antimicrobial culture data.

6.3 Study Population

6.3.1 Population Characteristics

The patient population were adult patients over the age of 18 admitted to the critical care units at both KNH and M.P Shah Hospital study sites.

6.3.2 Case Definitions

Definitions for Infection Sepsis and Septic Shock

Infection: Clinical and/or laboratory and/or radiological evidence of infection as per the ISF definitions (16).

Sepsis: Presence of infection and a SOFA score of 2 points or more or an increase in the baseline SOFA score by 2 or more points consequent to an infection (16).

Septic Shock: Sepsis plus cardiovascular instability as evidenced by a mean arterial pressure less than 65mmHg despite an intravenous fluid challenge of 30ml/kg, necessitating the use of vasopressors (53,54)

Specific Definitions for Infections

The International Sepsis Forum (ISF) consensus definitions were used to define infections as per specific definitions outlined below (1,2).

For Ventilator-associated pneumonia, a definition used by Madani et al (55) was chosen for its ease of use. Definitions on Central Nervous system infection were added by the primary investigators as this did not feature in the ISF definitions.

Infections were classified as either:

- Community-Acquired: Patients admitted from home with an infection or those who developed infections within 48 hours of admission (10).
- CCU acquired: Patients who developed an infection in the critical care unit 48 hours after admission (10).

Specific definitions used for categorization of infections were as follows:

1) **Respiratory**:
   a) Radiographic infiltrate plus the presence of fever and two of the following: Purulent sputum, cough, leukocytosis >11000, sp02 less than 90% on room air, or need for supplemental oxygen (32).
   b) **Ventilator-associated pneumonia**: 48 hours after endotracheal intubation plus the following criteria: Chest radiograph or CT scan that demonstrates new or worsening infiltrates, consolidation, cavitation, or pleural effusion and at least 1 of the following:
      i) New onset of purulent sputum or change in character of sputum;
      ii) Positive blood cultures or organism isolated by tracheal aspirate, bronchial brushing, bronchoalveolar lavage, or lung biopsy (55).
2) **Uro-sepsis**:
   a) Two of the following: Fever>38, frequency, urgency dysuria or suprapubic tenderness PLUS any one of:
      i) Positive urine analysis (dipstick) for leukocyte esterase or nitrates.
      ii) Pyuria (>10 wbc/microliter or >3 wbc/hpf
      iii)Positive Gram stain for causative microorganisms
      iv)2 urine cultures with repeated isolation of the same uropathogen of $>10^2$ cfu/ml
      v) 2 urine cultures demonstrating $<10^5$ of a single causative organism in a patient on antimicrobial therapy

3) **Skin and skin structure related infections including Surgical site infection**

Either one of the two criteria below:

- Positive Gram stain or culture of a microorganism from a surgical wound, purulent skin lesion, skin or soft tissue aspirate or biopsy.
- Clinical evidence such as spreading erythema, blanching, or purulent drainage from a surgical wound PLUS either one of:
    - Fever >38.0°C
    - Leukocytosis >11000.

4) **Intra-abdominal sepsis:** This was classified into the following: (See appendix 7 for specific definitions of each)

a) Primary, Secondary or Tertiary Peritonitis,

b) Intra-abdominal abscess

c) Biliary tract infections

d) Pancreatic infection

e) Typhlitis,

f) Toxic megacolon.

Diagnosis of each (except for pancreatic infections) required a compatible clinical presentation with systemic signs and symptoms such as fever (>38) and/or radiologic or surgical evidence of infection with/without microbiologic evidence such as blood cultures, peritoneal fluid microscopy or through direct aspiration of an abscess.

5) **Intravascular catheter-related sepsis:** Presence of indwelling central venous catheter in a patient with sepsis or septic shock and bacteremia based on either positive blood cultures and/or positive catheter tip cultures and/or clinical features such as erythema, cellulitis, pus from the catheter entry site.

6) **Bloodstream infections (BSI)**

   a) Micro-organism not regarded as a skin commensal, (Diptheroids, Bacillus species, Propionibacterium, Coagulase negative Staphylococci, or Micrococci) cultured from one or more blood cultures OR two or more positive blood cultures for a common skin contaminant.

   b) Infective Endocarditis: The Duke criteria (See Appendix Six) was used for the diagnosis of infective endocarditis. This was based on major and minor criteria. Infective endocarditis was be diagnosed in patients who met the following clinical criteria:

      i) Two major criteria OR

      ii) One major and three minor criteria OR

      iii) Five minor criteria

7) **CNS infections**

   a) Bacterial Meningitis: Two out of four of: Headache, fever, neck stiffness, and altered level of consciousness (GCS<15) and CSF biochemistry findings showing glucose <2/3rd of blood glucose, elevated proteins >45g/dl and/or organisms on CSF microscopy (40). A positive CSF GeneXpert, CSF Ziehl Neelsen stain for acid-alcohol fast bacilli was used to diagnose Tuberculous meningitis. A positive CSF Cryptococcal Antigen test was used to diagnose Cryptococcal meningitis. (56,57)

   b) Encephalitis: Altered mental state >24 hours with three of the following: (58)

      i) Fever >38 C

      ii) Partial or Generalized convulsions not attributable to an underlying seizure disorder

      iii) Focal neurologic findings that are new in onset

      iv) CSF white cell count > 5/cubic mm

      v) Neuroimaging suggestive of encephalitis

      vi) Abnormality on Electroencephalogram that suggests encephalitis

8) **More than one infection: T**he presence of 2 or more infections in the same patient (10).
9) **New infection:** Presence of an infection at a different anatomic site from the existing site.
10) **Polymicrobial infection:** Isolation of 2 or more microorganisms from the same site of infection.

Other Definitions

1. Fever: Core body temperature greater than 38.3 degrees Celcius. (59)

6.3.3 Inclusion and Exclusion Criteria

Inclusion Criteria

- Adult patients over the age of 18 years admitted to the CCUs.
- Signed and informed consent by either the patient or next of kin to participate in the study.

Exclusion Criteria

- Re-admissions to CCU's within a one- month period from CCU discharge.
- Covid-19 positive patients (positive test ascertained by RT-PCR based assay)

6.4 Sample Size Determination

The sample size formula for estimating prevalence developed by Cochran was used to determine the number of subjects to be included in the study. (60)

This formula is defined as:

$$n_0 = \frac{z^2\pi(1-\pi)}{\delta^2}$$

Where *z* is the level of significance=1.96,

π is the expected prevalence= (15%,44%,18%,29%)

δ is the margin of error= 0.05

n_0 is the sample size without considering the finite population correction factor.

To get the actual sample size for the study, *n,* the finite population factor 'N' was applied which was the expected total number of CCU patients within three months in KNH (n=115). The sample size using the finite population correction factor (N) was determined using the formula:

$$n = \frac{n_0 N}{n_0 + (N-1)}$$

Known prevalence and incidence rates of infections and sepsis were used in the formula.(2,10,61). The final minimum sample size was chosen as the maximum number of

subjects after adjusting for a 5% non-response rate. The table below shows the number of subjects for different prevalence and incidence values from other studies.

Table 2: Prevalence of infection and sepsis

Outcomes	Study	Estimated prevalence	Sample size	Estimated incidence	Sample size
Infection	1	15%	76	14.5%	76
	2	44%	**93**	12%	71
Sepsis	1	18%	80	13%	73
	2	29%	89	11.6%	70

In conclusion, a minimum of 93 participants were needed from KNH to compute stable prevalence and incidence rates of infections and sepsis..

A minimum additional 40 patients were needed from M.P. Shah based on the total number of patients expected over three months. An estimated 13 patients per month were expected.

The total sample population estimated was therefore 133 subjects with 93 from KNH and 40 from MPSH.

6.5 Sampling Methods and Patient Screening

Consecutive sampling methods were undertaken daily where all patients admitted to the CCU's were evaluated against the inclusion and exclusion criteria. Those that meet the specified case criteria and provided informed consent were recruited into the study.

Patient recruitment continued after the minimum sample size had been attained and ceased once the data collection period had ended to enable accurate computation of three- month period prevalence and incidence rates.

6.6 Recruitment and Consenting Procedure

Patients admitted to the CCU's were recruited on a daily basis by the primary investigator and research assistants within 24 hours of admission. For patients able to sign a consent form, consent was obtained directly from the patient. For patients that were unable to provide informed consent, consent was obtained from the next of kin. Subjects or next of kin received an explanation of the study aims, design, and potential benefits or risks if any. Once consent

was obtained subjects were recruited into the study. Consent was also taken to allow the researcher to contact the patient or designated next of kin at 28 days.

6.8 Flow Chart of Screening and Recruitment

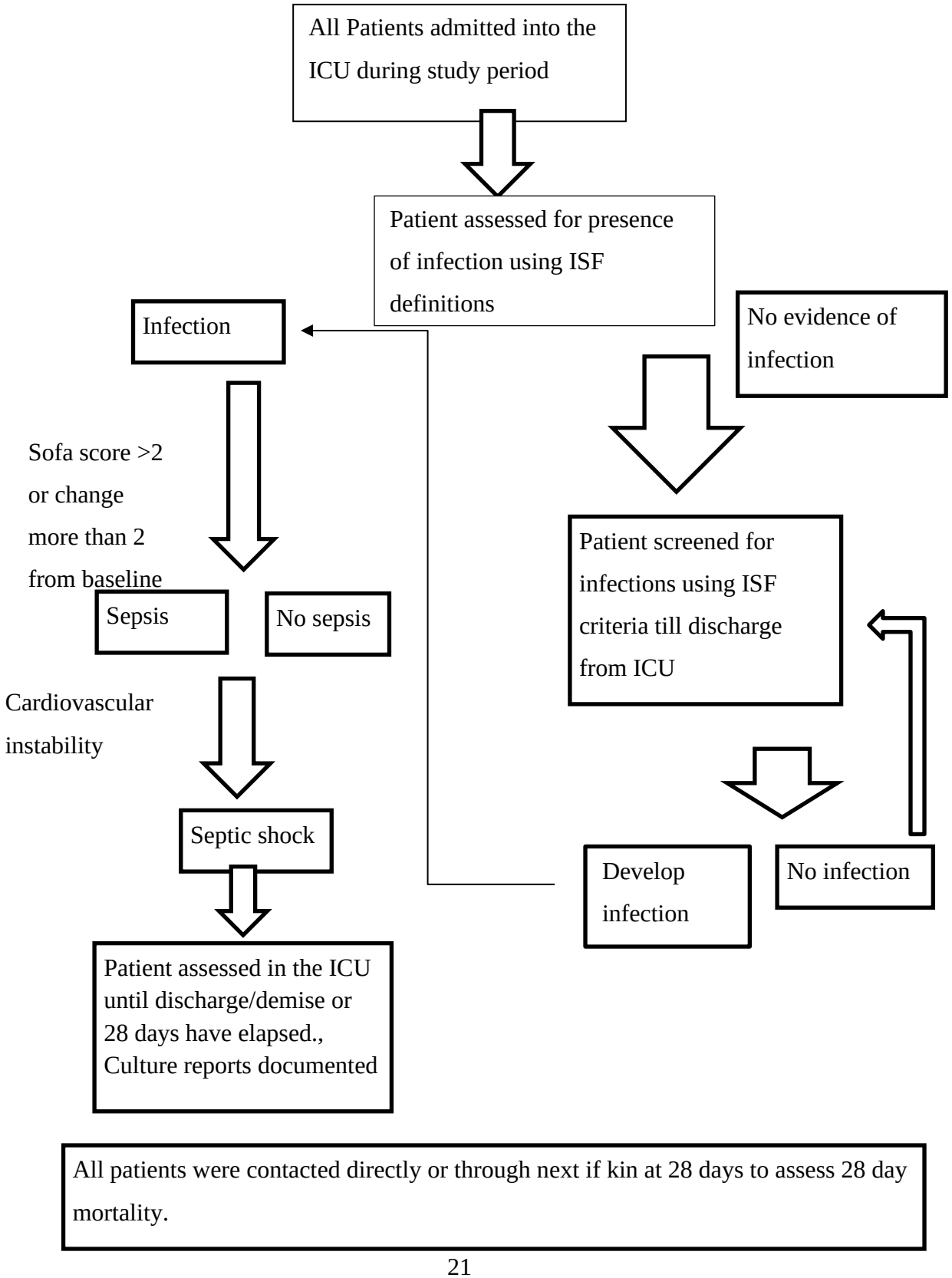

Figure 1: Patient Screening and recruitment

6.9 Study Variables

The study was a prospective observational study done over four months. Data collection was done by the primary investigator and research assistant through use of a case report form. Data was collected from all recruited patients who met the inclusion criteria and provided informed consent.

Admission data included diagnoses, biodata, co-morbidities, and vital signs. Patients were evaluated for infections using the ISF case definitions and those with infections were subsequently screened for sepsis using the SOFA score. Patients were then stratified into the following categories:

- No infection. These patients did not meet the ISF case criteria for infection. A baseline SOFA score was calculated on admission to assess for pre-existing organ dysfunction and subjects subsequently screened during CCU stay for evidence of incident infections, sepsis or septic shock.
- Infection but no sepsis. These patients met the ISF definitions for infection but had a SOFA score of less than 2 on admission. Primary foci of infection were categorized according to the ISF case definitions. For example: A patient admitted with pneumonia with a SOFA score of 1.
- Sepsis: as evidenced by presence of an infection as per the ISF definitions and a SOFA score >2, or an increase in SOFA score by 2 points from a previous baseline.
- Septic shock: evidenced by sepsis and a mean arterial pressure less than 65mmHg necessitating use of norepinephrine >0.1mcg/kg/min despite a 30ml/kg fluid bolus.

After admission to CCU's, all study subjects were then followed up during their CCU stay on day 2, 4, 7, 10, 14, 21 and 28 to assess for the following outcome variables:

a) Development of infection(s) in previously un-infected patients with documentation of the primary focus of infection as per the ISF criteria.
b) Development of new infections in a patient with an existing infection.
c) Development of sepsis through screening with the SOFA score.
d) Development of septic shock.
e) 28-day vital status (Alive or Dead).
f) Documentation of antimicrobial culture and sensitivity reports for organisms isolated.

Recurrent infections were not considered in this study. Only Index CCU admissions were included and patients discharged from and subsequently re-admitted to CCU's were excluded. Discharged patients were contacted directly through the telephone to ascertain vital status.
For subjects who were still admitted in the CCU's 28 days after admission, follow up ceased at day 28.

6.10 Data Collection Procedures

Data collection was done by the primary investigator and a research assistant. The research assistant was a trained Medical Officer with critical care work experience who was subsequently trained by the primary investigator on use of the SOFA score, the ISF case definitions and correct filling of the case report form. Data was collected through the use of a CRF which captured data from the patient's file, observation charts, nursing notes, fluid charts, laboratory reports, and radiological reports.
If a certain parameter was missing, the primary investigator attempted to obtain the value needed for example by tracking reports from the laboratory. If this was not possible, the patient was excluded from the study.

Data was collected on the following days:

- On admission (Day 0)
- Day Two (Within 48 hours upon admission)
- Day Four
- Day Seven
- Day Ten
- Day Fourteen
- Day Twenty-One
- Day Twenty-eight

Information on the following was collected:

A) Patient Biodata:
    i. Data on inpatient numbers, age, weight, gender, and whether the patient was admitted from home, another hospital or another ward within the hospital.
    ii. Telephone contact and designated next of kin contact
    iii. Location: M.P shah ICU (MPSH-I), M.P Shah HDU (MPSH-H), KNH Main ICU(KNH-I), KNH 7th floor MICU (KNH-MICU 7), KNH 8th floor
    iv. MICU(KNH-MICU8).

B) Clinical Information

Specific clinical data such as diagnoses, co-morbidities, vital signs, and vasopressor use were collected to identify patients with sepsis or septic shock. ISF definitions were used to screen for infections and categorize infections according to the primary foci. Laboratory results that were needed to compute the SOFA score were recorded and the SOFA score calculated at each interval.

Information collected from all patients included:

- Diagnostic data
    1. Admission Diagnosis
    2. Co-morbidities (Known that the patient is aware of or receiving treatment for)
    3. History of recent surgery (in last 30 days)
    4. Mechanically ventilated on admission
    5. Fraction of inspired oxygen (FI02)
    6. Receiving vasopressors or inotropic support. The specific inotropic agent will be recorded
    7. Volume and type of IV fluids received
    8. Glasgow Coma scale on admission
    9. Presence of invasive devices such as intravascular catheters
- Vital Signs
    1. Mean arterial pressure (mmHg) If more than one reading was taken, an average will be taken
    2. Temperature (Degrees Celsius) - The maximum temperature recorded will be used
    3. Oxygen saturation (Spo2%)
    4. Supplemental oxygen in liters or Fi02 for ventilated patients
- Laboratory Data.
    1. Arterial Pa02
    2. Total White blood cell count
    3. Neutrophil count
    4. Platelet count
    5. Total Bilirubin
    6. Creatinine

6.10.1 Use of the SOFA Score to Identify Patients with Sepsis

The SOFA score was used to identify patients with sepsis. It was applied to all patients within 24 hours on admission using the most recent laboratory values available. All patients with infections were screened for development of sepsis as evidenced by an increase of 2 points from the previous baseline SOFA score.

For patients who have been transferred to the CCU from the ward, the baseline SOFA score was calculated using laboratory values taken on admission to the hospital to assess for baseline organ dysfunction. The SOFA score was then calculated on admission to CCU using the most recent values available to screen for sepsis.

***Table 3: Sequential Organ Failure Assessment score (SOFA)*(24)**

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

6.10.2 Microbiologic Culture Reports

Microbiologic Data

i. A record was made at admission on the culture samples that have been taken from each patient. If no culture samples were taken, this was indicated. If new culture samples are taken after admission, the date and type of sample taken was recorded.

ii. Microorganisms isolated and antibiotic susceptibility patterns were noted in the data collection form. If culture samples were taken but no results were available at 28 days this was labeled as a "Missing result".

iii. Culture reports with documented contaminants reported by the laboratory will be excluded. The ISF case definitions for specific infections will be used to determine whether organisms are contaminants or colonizers.

6.10.3 Assessment of 28 Day Mortality

All patients in the CCU'S were followed up at 28 days via telephone contact to ascertain vital status. Consent was also obtained from the patient or next of kin to contact them at 28 days to assess vital status.

6.10.4 Data Collection Aids

Conversion tables were provided in the CRF to estimate FI02 from various oxygen delivery systems in patients who were not mechanically ventilated. The SOFA score was also included for ease of reference. A reference sheet for the ISF case definitions for infections was also provided.

6.10.5 Equipment

The equipment used in the study were as follows:

- Writing Stationery
- Calculator

No specialized equipment was used in the study.

6.10.6 Quality Assurances

The research team consisted of the primary investigator, supervisors, a trained research assistant as well as a statistician.

The primary investigator oversaw the training of the research assistant in proper filling of the case report form and use of data collection tools and aids. Weekly meetings were held with the research team to identify and address any irregularities in data collection.

7.0 ETHICAL CONSIDERATIONS

The study was carried out after obtaining approval by the Department of Clinical Medicine and Therapeutics, University of Nairobi, Kenyatta National Hospital/University of Nairobi Ethics and Research Review Committee (KNH/UON-ERC) and hospital administration at M.P. Shah Hospital.

Participants were recruited voluntarily. Informed consent was obtained from all eligible participants. Consent was also obtained to contact the participants or next of kin at 28 days. For patients too sick to provide informed consent, the next of kin or legal proxy was approached. The research team ensured that patient confidentiality was maintained at all times and patients were free to withdraw from the study at any time. The study was purely observational; no investigations were requested for or carried out by the principal investigator. Patient management was not influenced by the primary investigator and remained the responsibility of the primary physicians responsible for patient management. All data obtained from this study was used for the sole purpose of meeting the objectives stated in this proposal.

8.0 DATA MANAGEMENT

All the research data was accessible by the researchers, PI and Co-Is and stored in a secure password protected database. All the documents were stored in secured offices accessible only to the researchers. All data was available for the research program duration of 12 months and then archived in line with data standards of the University of Nairobi. All hard copies of the data collection forms were scanned and stored electronically in line with institutional standards and then destroyed. No identifiable personal or demographic data was used. Data was stored electronically on a password protected server.

8.1 Statistical Analysis

Frequency (percentages) were used to summarize the prevalence and incidence of infection and sepsis. Incidence densities for episodes of infection and incidence rates at specific time intervals for infections, sepsis and septic shock were calculated. Prevalence rates were calculated as the number with the event of interest (infection, sepsis) divided by the total sample size. Incidence rates were computed as the proportion of patients who developed the outcome of interest. Case fatality rates were calculated as the number of patients who died divided by the population. This was done for patient populations with no infection, patients with sepsis and patients with septic shock.

Wald 95% confidence intervals around the prevalence, incidence, and mortality rates were also calculated.

Foci of infection were tabulated using frequency distribution tables and presented using bar charts.

The analysis was stratified by the hospitals (KNH and MP Shah) and chi-squared tests were used to determine statistically significant differences in prevalence, incidence and mortality rates. Analysis was also done for the combined sample population.

The antimicrobial culture data was analyzed as a combined data set for each type of culture specimen to determine common causative organisms. Antibiotic susceptibility and resistance patterns were then tabulated.

Table 4: Table to illustrate statistical analysis

Objective	Data Collected	Source of Data	Method of Data Analysis
Primary Objective 1,2	Numbers of patients admitted with infection, sepsis	Patient file, nursing charts	Proportions and confidence intervals to calculate incidence and prevalence rates
Primary Objective 3	Vital status at 28 days	Direct telephone contact	Proportions to calculate case fatality rate
Secondary Objective 1	Antimicrobial culture data	Specimen culture reports	Tables
Secondary Objective 2	Foci of infection classified as per case definitions	Patient file, nursing charts, laboratory reports	Bar graphs to show proportions of infections seen.
Secondary Objective 3	Antimicrobial culture data	Specimen culture reports	Antibiogram
Secondary Objective 4	Number of patients with septic shock, vasopressor use, lactate levels	Nursing charts, clinician notes	Proportions and confidence intervals to calculate incidence and prevalence rates

9.0 IMPACT OF COVID-19 ON DATA COLLECTION

Due to the impact of COVID-19 in healthcare facilities, certain measures were assessed to ensure minimal impact on data collection and safety of the primary investigator and research assistant.

1. The KNH main CCU and both Medical ICU's used in the study did not admit COVID-19 positive patients. These patients were admitted in the isolation facility at the hospital. Data collection on sepsis was able to proceed with minimal interruption.
2. M.P. Shah Hospital also had a separate COVID-19 unit. ICU/HDU facilities for COVID-19 positive patients were separate from NON-COVID patients.
3. Both facilities provided adequate Personal protective equipment (PPE) for healthcare workers in all the critical care units.
4. Routine testing of suspected patients with fast turnaround time of results was routinely done in critical care units at both facilities with prompt isolation and transfer of suspected and positive cases for isolation.

5. COVID-19 patients were excluded from the study for several reasons. Firstly, to minimize the risk of infection to the investigators during data collection. Secondly, at the time of the study, COVID-19 being a new and relatively poorly understood infection would have posed challenges in distinguishing bacterial sepsis from COVID-19 related illness. Subjects who were diagnosed with COVID-19 after admission to the CCU's were also excluded from the study.

Therefore, data collection for this study was able to proceed with minimal adverse impact from COVID-19.

10.0 RESULTS

Between the months of December 2021 and February 2021, a total of 172 critical care admissions from KNH and MP SHAH Hospital (MPSH) Critical care units (CCU's) were sequentially screened for eligibility. Of these, 8 subjects were excluded as they were under the age of 18 and 4 subjects declined to provide informed consent. A total of 160 subjects (108 from KNH and 52 from MPSH) were recruited into the study and subsequently screened using the ISF consensus definitions and SOFA scores for infection, sepsis and septic shock. The screening exercise was repeated at day 2, 4, 7, 10, 14, 21 and 28 to identify incident cases. (Figure 4)

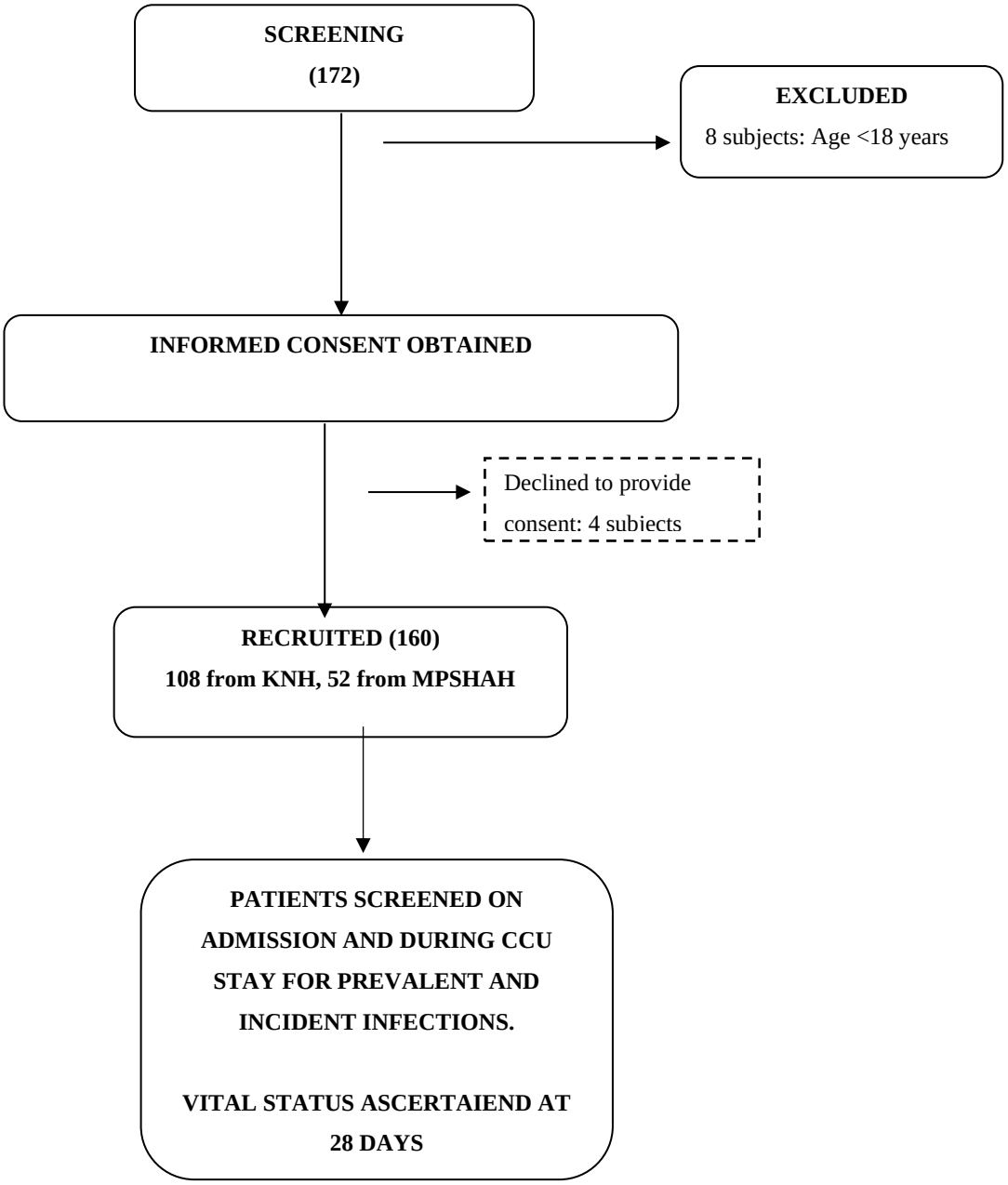

Figure 2: Flowchart of patient screening and recruitment

10.1 Demographic Information

Among subjects in the combined sample, 61.2% of subjects were male, 38.8% were female. The mean age was 45.8 years and the range was between 18 and 93 years. The median age was 44.5 years with an interquartile range (IQR) of 30-59 years.

Among subjects in the KNH sample, 63.9% of subjects were male and 36.1% were female. The mean age at KNH was 40 years and the range was between 18 and 86 years. The median age was 38 years with an IQR of 28-49.5 years.

Among subjects in the MPSH sample, 56% of subjects were male and 44% female. The mean age at MPSH was 56.9 years and the range was between 21 and 93 years. The median age was 58 years with an IQR of 46.5-72.5 years. When the two sample populations were compared, the average and median ages among the KNH cohort were significantly lower than the MPSH cohort. ($p<0.001$)

Among the KNH sample, 52.8% of admissions were in-hospital ward transfers, 36.1% were admitted from home as de-novo admissions and 11.1% were external transfers from a peripheral health facility. At MPSH, 15.4% of subjects were in-hospital ward transfers, 80.8% were admitted from home as de-novo admissions, and 3.8% were external transfers from a peripheral health facility. Furthermore, significantly larger proportion of patients in the KNH cohort compared to the MPSH cohort were admitted either directly from home or transferred from another hospital ward. ($p<0.001$)

The average CCU length of stay (LOS) in the combined sample was 8.3 days. The LOS in the KNH cohort (9.3 days) was significantly longer than the LOS in the MPSH cohort (6.3 days) ($p<0.001$)

(Table 6)

Table 5: CCU patient demographic

		Sites		P value
Variables	**Combined**	**KNH**	**MPSH**	
	% (n=160)	% (n=108	% (n=52)	
Sex				
Male	61.2% (98)	63.9% (69)	55.8% (29)	0.3234
Female	38.8% (62)	36.1% (39)	44.2% (23)	0.3234
Average Age (years)	45.8(SD:18.9)	40.4(SD:16.2)	56.9(SD: 19.3)	< 0.001
Median Age (years)	44.5	38	58	< 0.001
Interquartile Age range (years)	30-59	28-49.5	46.5-72.5	
Source of admission:				
Home	50.6% (81)	36.1% (39)	80.8% (42)	< 0.001
In hospital Transfer	40.6 % (65)	52.8 % (57)	15.4 % (8)	< 0.001
External transfers	8.8 % (14)	11.1 % (12)	3.8 % (2)	0.1277
Average Length of ICU stay (days)	8.3 (SD:8.4)	9.3 (SD: 9)	6.3 (SD:6.8)	< 0.001

P value: Computed to compare the KNH versus MPSH sample cohorts.

10.2 Admission Diagnoses and Co-morbidities

Among the combined sample, 53.1% of CCU admission diagnoses were medical, 32.5% were neurosurgical, and 13.1% were general surgical.

Among subjects in the KNH sample, 44.4% of subjects were admitted with a medical diagnosis, 42.6% with a neurosurgical diagnosis and 12% admitted with a general surgical diagnosis. Among the medical patients, the top three etiologies were diabetic ketoacidosis at 12.9%, pneumonia at 7.4% and meningitis at 5.6%. Among neurosurgical etiologies, severe head injury accounted for the majority at 74% whereas peritonitis was the most common surgical etiology at 2.8%.

Among subjects in the MPSH sample, 71.2% of subjects were admitted with a medical diagnosis, 11.5% with a neurosurgical diagnosis and 15.4% with a general surgical diagnosis. Among the medical patients, the top three etiologies were pneumonia at 13.5%, myocardial infarction and diabetic ketoacidosis at 9.6% Among the neurosurgical patients, severe head injury accounted for 33% whereas among general surgical subjects, peritonitis was the most common etiology at 5.7%. (Table 7 and Figure 4)

Upon comparing the two samples, the KNH cohort had a significantly smaller proportion of medical admissions (44.7% vs 71.2%) (p=0.0015) and a significantly larger proportion of neurosurgical admissions (42.6% vs 11.5%) (p=0.0001).

Co-morbidities were defined as any distinct additional morbidity present on admission separate from the admitting diagnosis. 61.9% of all critical care admissions had one or more co-morbidities. Among subjects with co-morbidities in the combined sample, diabetes (insulin and non-insulin dependent) accounted for 31% followed by hypertension at 30%, malignancies at 15% and retroviral disease infection at 14%. This is illustrated in Figure 5.

Among subjects with co-morbidities in the KNH sample, hypertension, diabetes (insulin and non-insulin dependent), retroviral disease infection and malignancies accounted for 30%, 29%, 21% and 15% respectively.

Among subjects with co-morbidities in the MPSH sample, hypertension, diabetes (insulin and non-insulin dependent), retroviral disease infection and malignancies accounted for 30%, 34%, 5% and 20% respectively. (Figure 5)

Table 6: Diagnosis on admission to critical care units

ADMITTING DIAGNOSIS	NO OF PTS COMBINED % (n=160)	NO OF PTS KNH % (n=108)	NO OF PTS MPSH % (n=52)	P values
Medical	53.1% (85)	44.4% (48)	71.2% (37)	0.0015
Neurosurgical	32.5% (52)	42.6% (46)	11.5% (6)	0.0001
General Surgical	13.1% (21)	12% (13)	15.4% (8)	0.5570
Obstetrics and Gynecology	1.3% (2)	0.9% (1)	1.9% (1)	0.5949
TOTAL	160	108	52	

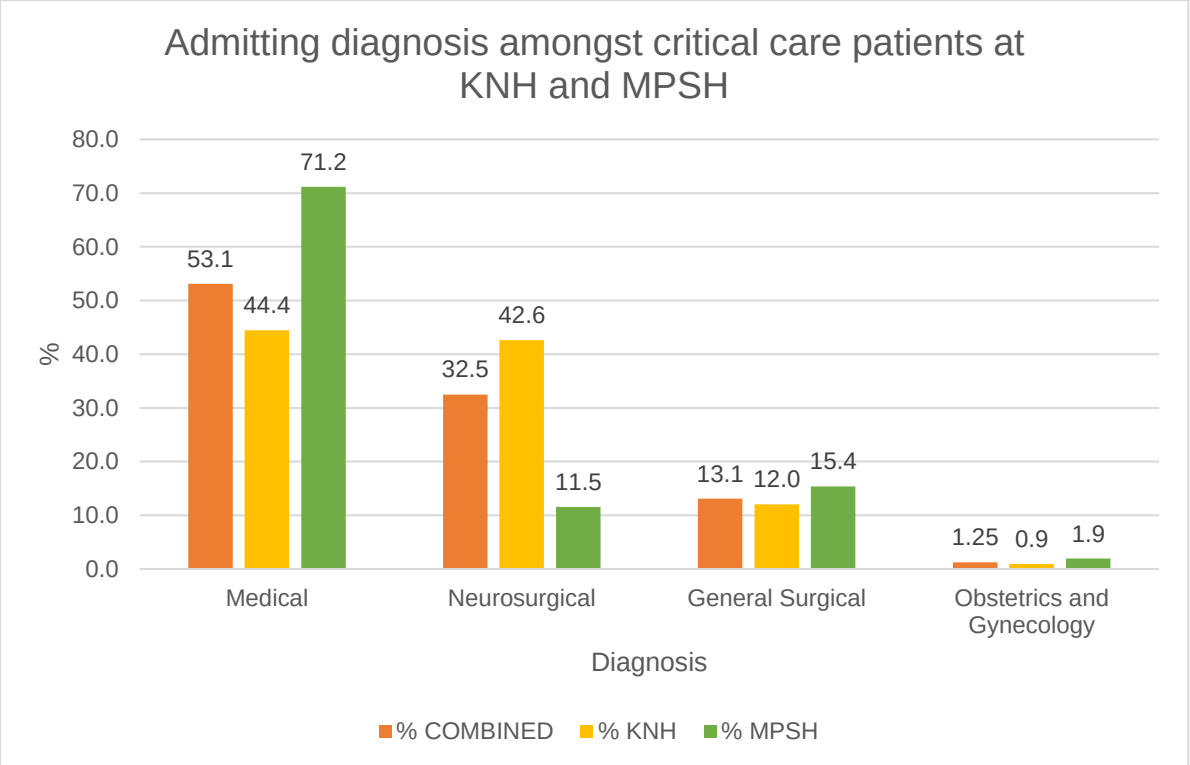

Figure 3: Bar chart showing patient diagnosis on admission to critical care units

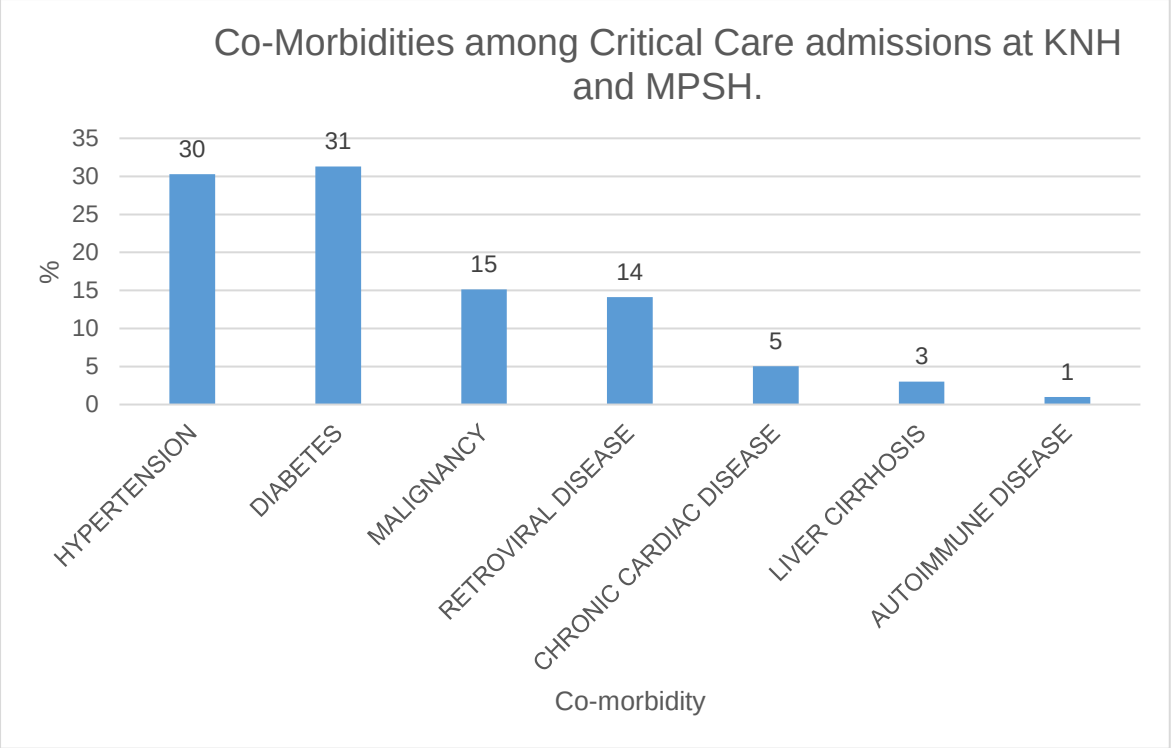

Figure 4: Bar chart showing co-morbidities among critical care patients in the combined sample cohort

10.3 Prevalence of Infections, Sepsis and Septic Shock

Subjects were screened on admission to the CCU'S for evidence of infection using the ISF consensus definitions. The SOFA score was then applied to all infected subjects to detect sepsis and septic shock. The prevalence of infection was computed as the proportion of patients from the total sample size with infection. Prevalence rates of sepsis and shock were computed as the proportion of infected patients with sepsis or shock.

In the combined sample, the prevalence of infection on admission to CCU was 52.5% (n =84; 95% CI: 44.5-60.4). The prevalence of sepsis was 35% (n=56; 95% CI: 27.63-42.93) and the prevalence of septic shock was 13.8% (n= 22; 95%CI: 8.82-20.07). Only 3.8% (n=6 95% CI: 1.39-7.98) of subjects with infection did not have sepsis.

At KNH, the prevalence of infection was 55% (n=60; 95% CI 45.9-65.1). All infected subjects had sepsis and the prevalence of sepsis was 38.9% (n= 42, 95%CI: 29.66-48.75) while the prevalence of septic shock was 16.7% (n=18; 95%CI 10.19-25.06).

At MPSH, the prevalence of infection was 46.2% (n=24; 95%CI 32.3-60.5). The prevalence of sepsis was 26.9% (n= 14; 95%CI 15.57-41.02) and the prevalence of septic shock was 7.7% (n=4; 95%CI 2.14-18.54). Among the MPSH sample 11.5% (n=6; 95% CI 4.35-23.44) had infection without sepsis.

When the two samples were compared, the difference in prevalence of infection between KNH (55.6%) and MPSH (46.2%) was not significant (p=0.3).

Furthermore, the difference in prevalence of sepsis at KNH (38.9%) and MPSH (26.9%) was not significant. (p=0.1). The difference in prevalence of septic shock at KNH (16.7%) and MPSH (7.7%) was also not significant (p=0.1).

The prevalence of subjects with infection (no sepsis) was significantly higher at MPSH (11.5%) compared to KNH (0%), (p=0.0003). This is illustrated in Table 8 and Figure 6.

Table 7: Prevalence of infections, sepsis and septic shock on admission to critical care units

Category	**Combined n-160 % (n) (95% CI)**	**KNH n-108 %(n) (95% CI)**	**MPSH n-52 % (n) (95% CI)**	**P value**
All Infections	52.5% (84) (44.5-60.4)	55.6% (60) (45.9-65.1)	46.2% (24) (32.3-60.5)	0.3
Infection (no sepsis)	3.8% (6) (1.39-7.98)	0	11.5% (6) (4.35-23.44)	0.0003
Sepsis	35% (56) (95% CI 27.63-42.93)	38.9% (42) (95% CI 29.66-48.75)	26.9% (14) (95% CI 15.57-41.02)	0.1
Septic Shock	13.8% (22) (8.82-20.07)	16.7% (18) (10.19-25.06)	7.7% (4) (2.14-18.54)	0.1

P value: Computed to compare the KNH versus MPSH sample cohorts.

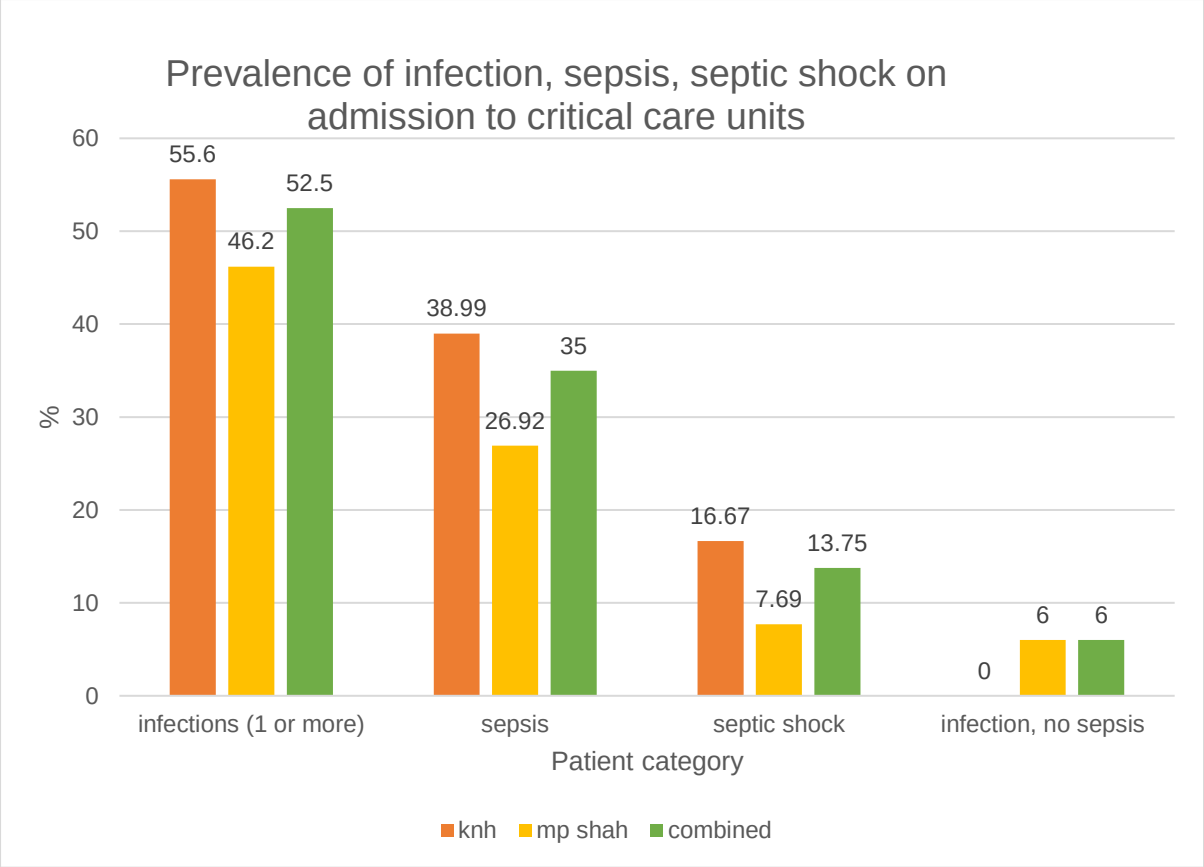

Figure 5: Bar chart showing the prevalence of infections, sepsis and septic shock in critical care units

10.4 Incidence of infections, sepsis and septic shock

All subjects were screened on day 2, 4, 7, 10, 14, 21 and 28 using the ISF case definitions for development of infections in the CCU's. The SOFA score was applied to all infected subjects at the same intervals to assess for development of sepsis and septic shock.

The incidence of infection was computed as the percentage of subjects in the sample who acquired one or more new infections during their ICU stay regardless of their infection state on admission divided by the total population. This was done as subjects admitted with infection(s) can acquire new infections. New infections among those with prevalent infection(s) were defined as infections at a remote anatomical site from a current infection site.

Incidence rates for sepsis and shock were computed as the percentage of subjects that developed sepsis or shock divided by the population at risk. The population at risk was computed by deducting prevalent cases from the total 'N'.

Among the subjects in the combined sample, the incidence of infection was 41.3% (n=66; 95% CI 33.5-49.3). Among these subjects, 57.6% (n=38) had a prevalent infection on admission. Only 42.4% (n=28) were infection free and hence developed a new infection in the CCU's. The incidence of sepsis and septic shock were 25.6% (n=21; 95%CI 16.6-36.4) and 11.6% (n=18; 95%CI 7.9-19.8) respectively.

Among the KNH sample, the incidence of infection was 50% (n=54; 95% CI: 40.2-59.8). Among these subjects 57% (n=31) had a prevalent infection at admission. The incidence of sepsis and septic shock was 37.5% (n=18; 95%CI 23.9-52.6) and 17.8% (n=16; 95%CI 10.5-27.3) respectively.

Among the MPSH sample, the incidence of infection was 23.1% (n=12; 95% CI 12.5-36.8). Among these subjects, 58% (n=7) had a prevalent infection on admission. The incidence of sepsis and septic shock was 8.9% (n=3; 95%CI 1.9-23.7) and 4% (n= 2; 95% CI 0.4-13.7) respectively

When the two samples were compared, the incidence of infections at KNH (50%) was significantly higher than MPSH (23.1%) (p=0.0012). The incidence of sepsis and septic shock at KNH (37.5%), (17.8%) was significantly higher than MPSH (8.9%), (4%), (p=0.0034), (p= 0.02) respectively. (Table 9 and Figure 7)

Table 8: Incidence of infections, sepsis and septic shock.

Category (patients)	**Combined** **% (n) (95% CI)**	**KNH** **% (n) (95% CI)**	**MPSH** **% (n) (95% CI)**	**p- value**
Infection (1 or more)	41.3% (66) (33.5 – 49.3)	50% (54) (CI 40.2-59.8)	23.1% (12) (12.5-36.8)	0.0012
Sepsis	25.6% (21) (16.6-36.4)	37.5% (18) (23.9-52.6)	8.9% (3) (1.9-23.7)	0.0034
Septic shock	13.0% (18) (7.9-19.8)	17.8% (16) (10.5-27.3)	4% (2) (0.4-13.7)	0.02

P value: Computed to compare the KNH versus MPSH sample cohorts.

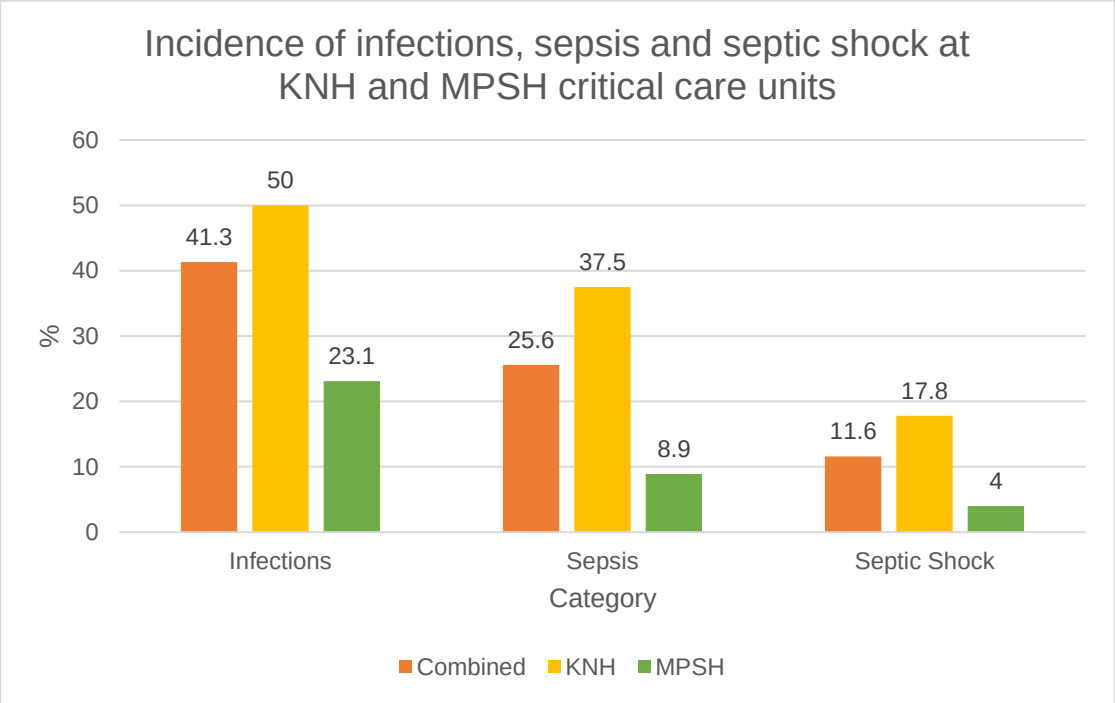

Figure 6: Bar chart illustrating the incidence of infections, sepsis and septic shock for the combined sample population

Subjects in critical care units can develop more than one episode of infection, and hence incidence density expressed as episodes of infection per 100 person ICU days was computed. A total of 80 incident episodes of infection occurred among the combined sample which computed to an ID of 18 episodes per 100 person days. At KNH there were 62 incident episodes of infection computing an ID of 18.1 episodes per 100 person days. At M.P. Shah there were 18 incident episodes of infection computing an ID of 17.7 episodes per 100 person days. This is demonstrated in Table 10.

Table 9: Incidence densities of infections in critical care units expressed as episodes of infection per 100 person days.

Center	ID (episodes per 100 person days)	95%CI
COMBINED	18 (80 cases)	14.55-21.92
KNH	18.1 (62 cases)	14.19-22.63
MPSH	17.7 (18 cases)	10.81-26.45

To demonstrate the time period during which incident episodes of infection, sepsis and septic shock occurred, incidence rates for infections, sepsis and septic shock were computed for the days at which subjects were screened for these events (Day 2, 4,7, 10, 14, 21, 28).

The peak incidence rate for infections was 17.2% occurring on day 4. (Figure 8).

The peak incidence rate for sepsis among patients who either had a prevalent or incident infection was 15.2% on day 7. (Figure 9)

The peak incidence rate for septic shock among patients who either had a prevalent or incident infection was 6 % on day 2 (Figure 10)

Figure 11 illustrates the incidence rates on infections, sepsis and septic shock at specific time points.

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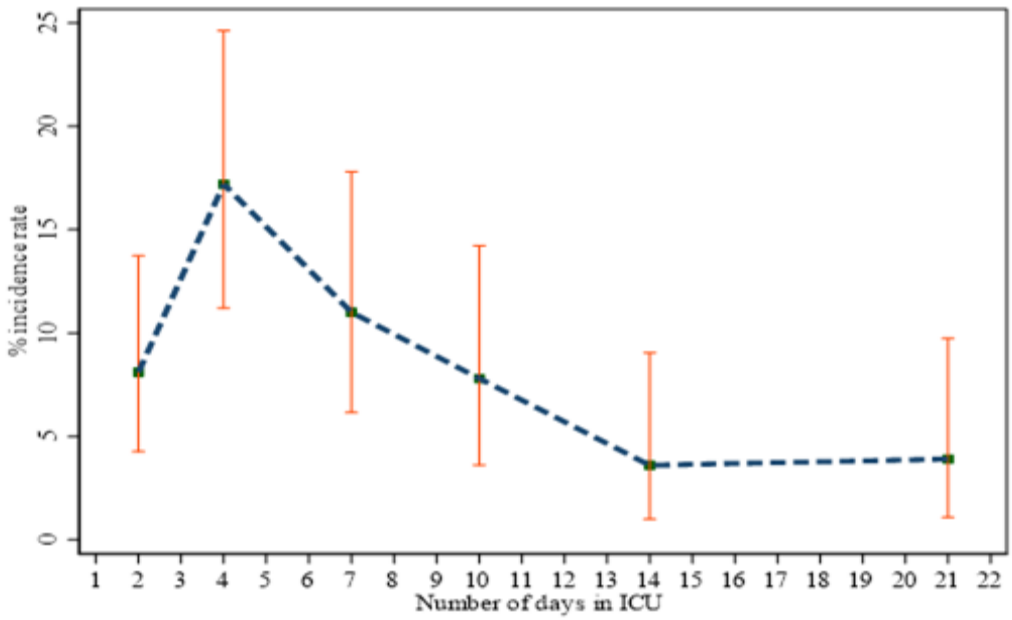

Figure 7: Line graph showing incidence rates of infection in critical care units at specific time points.

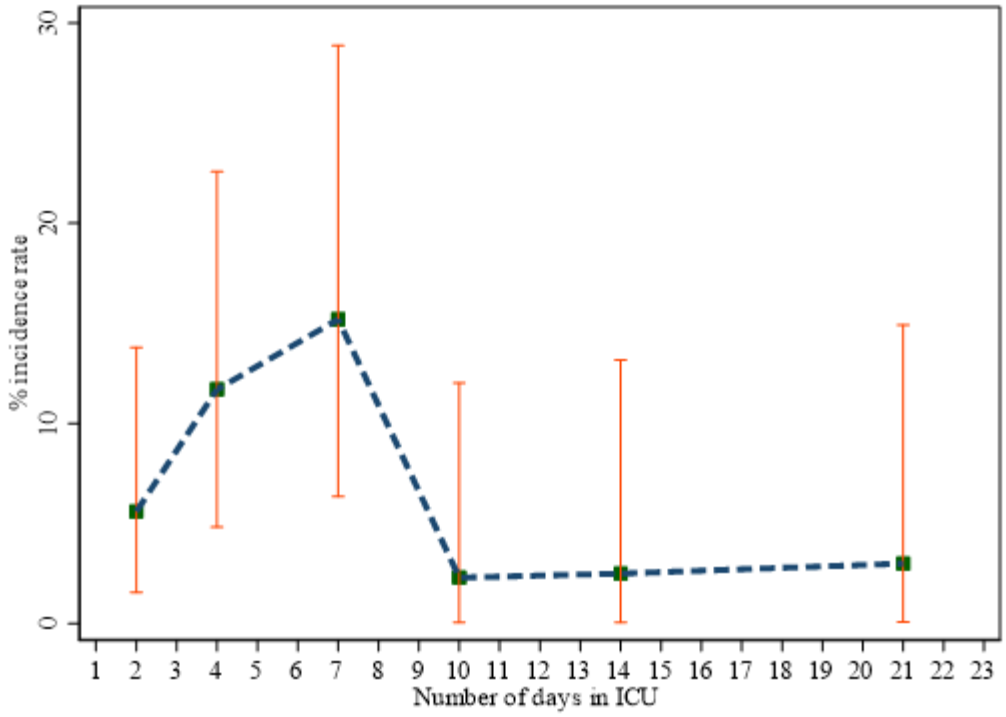

Figure 8: Line graph showing incidence rates of sepsis in critical care units at specific time points.

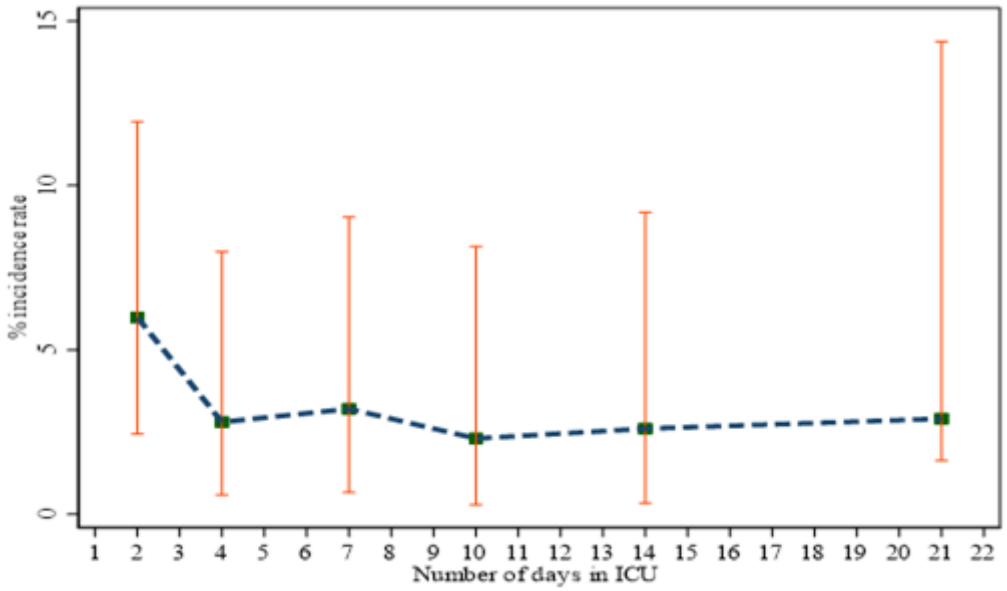

Figure 9: Line graph showing incidence rates of septic shock in critical care units at specific time points.

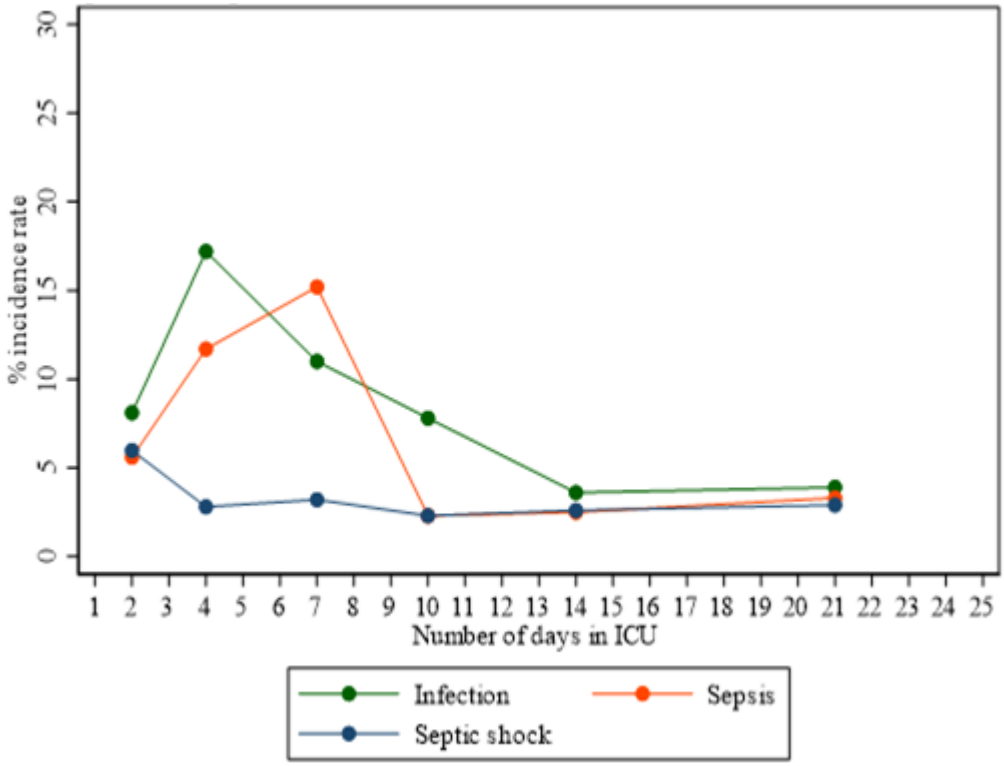

Figure 10: Line graphs showing incidence rates of infection, sepsis and septic shock at specific time points during CCU stay.

10.5 Case Fatality rates

Case fatality rates were computed for the study populations in each hospital.
A total of 62 mortalities occurred in the combined sample population (N=160), 50 from the KNH cohort and 12 from the MPSH cohort. The Case fatality rate (CFR) for the combined sample population was 38.8% (n=62; 95% CI: 31.2-46.8).
The CFR for the KNH sample cohort was 46.3% (n=50; 95% CI 36.7-56.2), compared to 23.1% in the MP Shah cohort (n=12; 95% CI 12.5-36.9) When the two sample cohorts were compared, The CFR in the KNH cohort was significantly higher compared to MPSH (p=0.0048). (Figure 12).

Among subjects without any incident or prevalent infection, the combined CFR was 27.1% (n=13; 95% CI 15.3-41.9). The CFR among the KNH cohort was 44% (n=11; 95% CI 24.4-65.1), whereas the CFR among the MP Shah cohort was 8.7% (n=2 95% CI 1.1-28.0).
Furthermore, the CFR in subjects without infection at KNH was significantly higher compared to MPSH (p=0.0060).

Among patients with infections, mortalities were only observed in subjects who were either in sepsis or septic shock. Among subjects with sepsis (either incident or prevalent), the combined CFR was 46.8% (n=36; 95% CI 35.3-58.5) The CFR among the KNH cohort was 46.7% (n=28; 95% CI: 33.7-60.0), whereas the CFR among the MPSH cohort was 47.1% (n=8; 95% CI: 23.0-72.2).
Among subjects with septic shock (either incident or prevalent), the combined CFR was 59.1% (n=13; 95% CI 36.4-79.3%. The CFR among the KNH cohort was 61.1% (n=11; 95%CI: 35.8-82.7), whereas the CFR among the MPSH cohort was 50% (n=2; 95%CI: 6.8-93.2).
There was no statistically significant difference between KNH and MPSH in the CFRs for patients with sepsis and septic shock. (Table 11 and Figure 13).

Among subjects in the combined sample, 79% of mortalities occurred in the CCU's, 27% occurred in the hospital ward and 3% occurred after patients had been discharged from hospital.
Among the KNH cohort, 80% occurred in the CCU's, 16% occurred in the hospital ward and 4% occurred after patients had been discharged from hospital.
Among the MPSH cohort, 75% occurred in the CCU's and 25% occurred in the hospital ward. (Table 12)

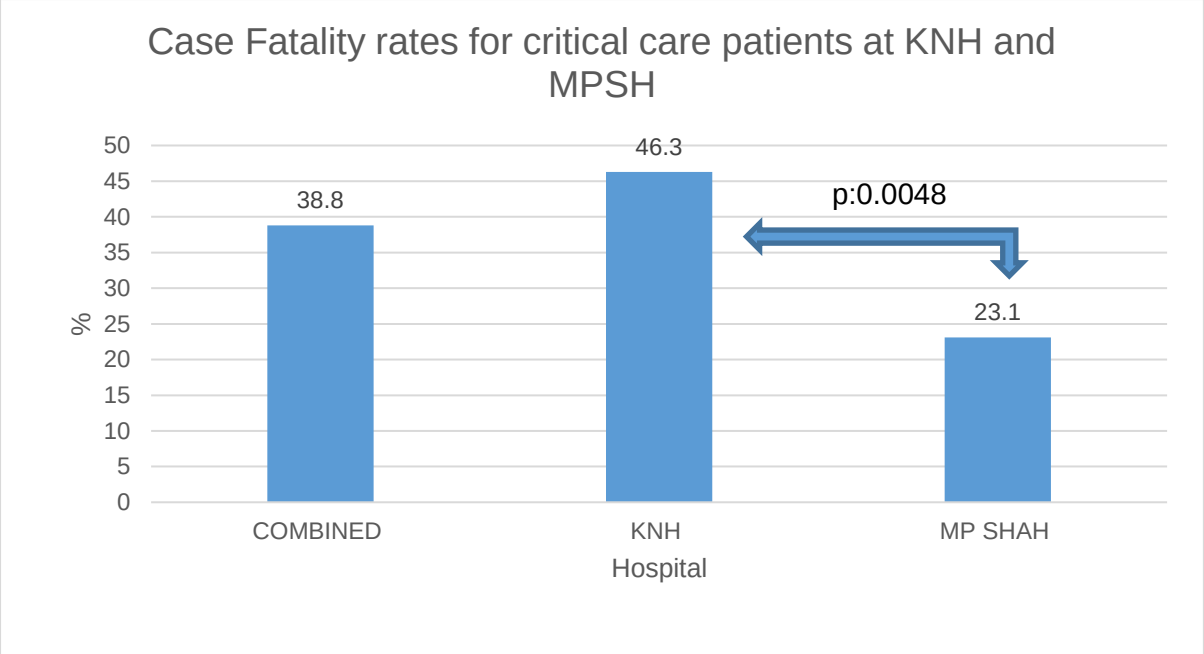

Figure 11: Bar chart comparing the Case fatality rate for critical care patients at KNH and MP Shah.

Table 10: 28-day Case fatality rates for all study subjects, subjects without infections, subjects with sepsis and septic shock.

	COMBINED % (95% CI)	**KNH % (95% CI)**	**MP SHAH % (95% CI)**	**p-value**
ALL STUDY SUBJECTS	38.8% (31.2-46.8)	46.3% (36.7-56.2)	23.1% (12.5- 36.9)	0.0048
NO INFECTION	27.1% (15.3-41.9)	44% (24.4-65.1)	8.7% (1.1-28.0)	0.0060
SEPSIS	46.8% (35.3-58.5)	46.7% (33.7-60.0)	47.1% (23.0-72.2)	0.9
SEPTIC SHOCK	59.1% (36.4-79.3)	61.1% (35.8-82.7)	50% (6.8-93.2)	0.7

P value: Computed to compare the KNH versus MPSH sample cohorts.

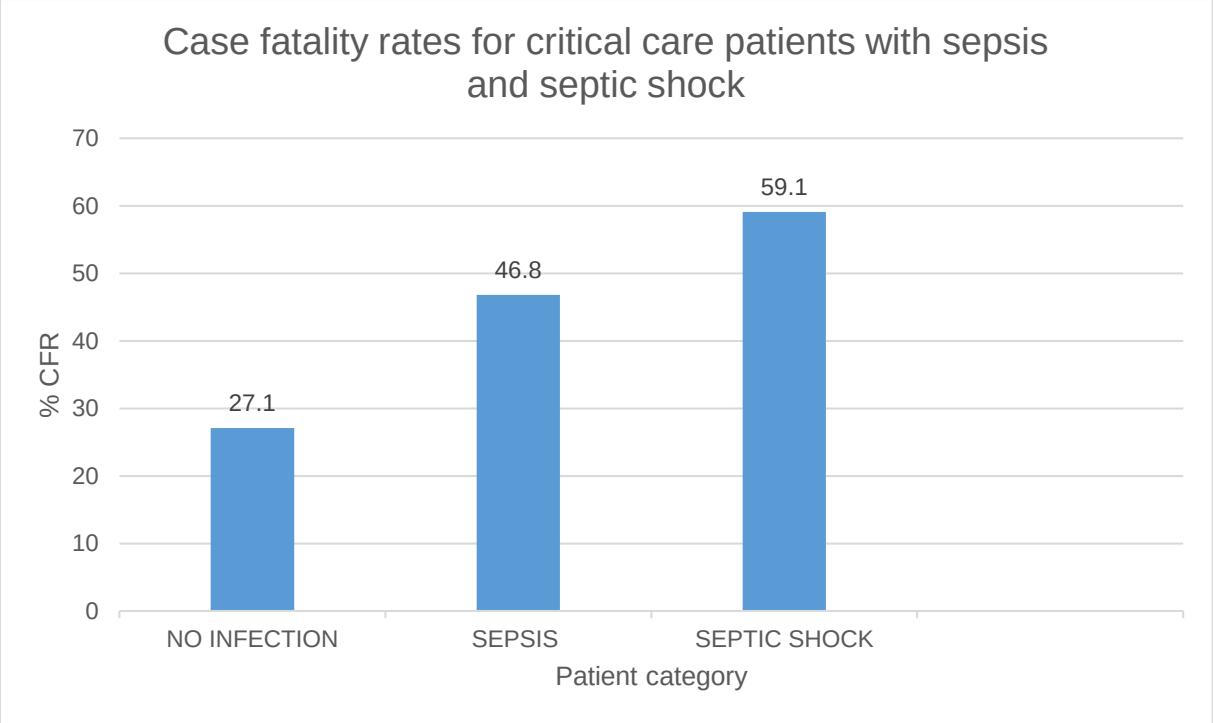

Figure 12: Bar chart comparing the 28- day case fatality rates for critical care patients with no infection versus sepsis and septic shock

Table 11: Proportion of In-CCU, In-Hospital and Out-of-hospital mortalities among critical care patients.

	Combined (frequency)	**KNH (frequency) %**	**MPSH (frequency) %**
Total mortalities	62	50	12
In-CCU mortalities	49 (79%)	40 (80%)	9 (75%)
In-Hospital mortalities	17 (27%)	8 (16%)	3 (25%)
Out-of hospital mortalities	2 (3%)	2 (4%)	0 (0%)

10.6 Foci of Prevalent Infections in Critical Care Units.

The ISF definitions of infections were used to classify infections according to foci which were tabulated and expressed as proportions.

On admission, among subjects in the combined sample, a total of 84 subjects had one or more prevalent infections. Among these 84 patients, 77.3% (n=65) had a single focus of infection while 22.7% (n=19) had multiple foci. Therefore, a total of 103 foci of infection were computed. Foci of prevalent infection were respiratory (48.6%), intra-abdominal (14.6%), central nervous system (13.6%), skin and skin structure (11.7%) and uro-sepsis (8.7%). No cases of blood-stream infections were observed.

At the KNH CCU's, 79%(n=60) of subjects had a single focus of infection while 21%(n=16) had multiple foci. Foci of infection were respiratory (54%), intra-abdominal infections (17%), central nervous system (24%), skin and skin structure (13%) and urosepsis (7%).

At the MPSH CCU's, 89% (n=24) of subjects had a single focus of infection while 11% (n=3) had multiple foci. Foci of infection were respiratory (33%), intra-abdominal (22%), central nervous system (4%), skin and skin structure (19%) and urosepsis (19%).

The above is illustrated in Table 13 and Figure 14.

Table 12: Foci of infection among prevalent cases of infection on admission to critical care units.

TYPE OF INFECTION	COMBINED DAY 0	DAY 0 KNH	DAY 0 MPSH
	FREQUENCY (%)	FREQUENCY (%)	FREQUENCY (%)
RESPIRATORY	50 (48.5%)	41 (54%)	9 (33%)
INTRA ABDOMINAL	15 (14.6%)	9 (17%)	6 (22%)
CNS INFECTIONS	14 (13.6%)	13 (24%)	1 (4%)
SKIN/ SKIN STRUCTURE	12 (11.7%)	7 (13%)	5 (19%)
URO-SEPSIS (excluding CAUTI)	9 (8.7%)	4 (7%)	5 (19%)
INTRA-VASCULAR CATHETER	2 (1.9%)	2 (4%)	0
CAUTI	1 (1%)	0	1 (4%)
TOTAL	103	76	27

CAUTI: Catheter associated urinary tract infection, CNS: Central nervous system

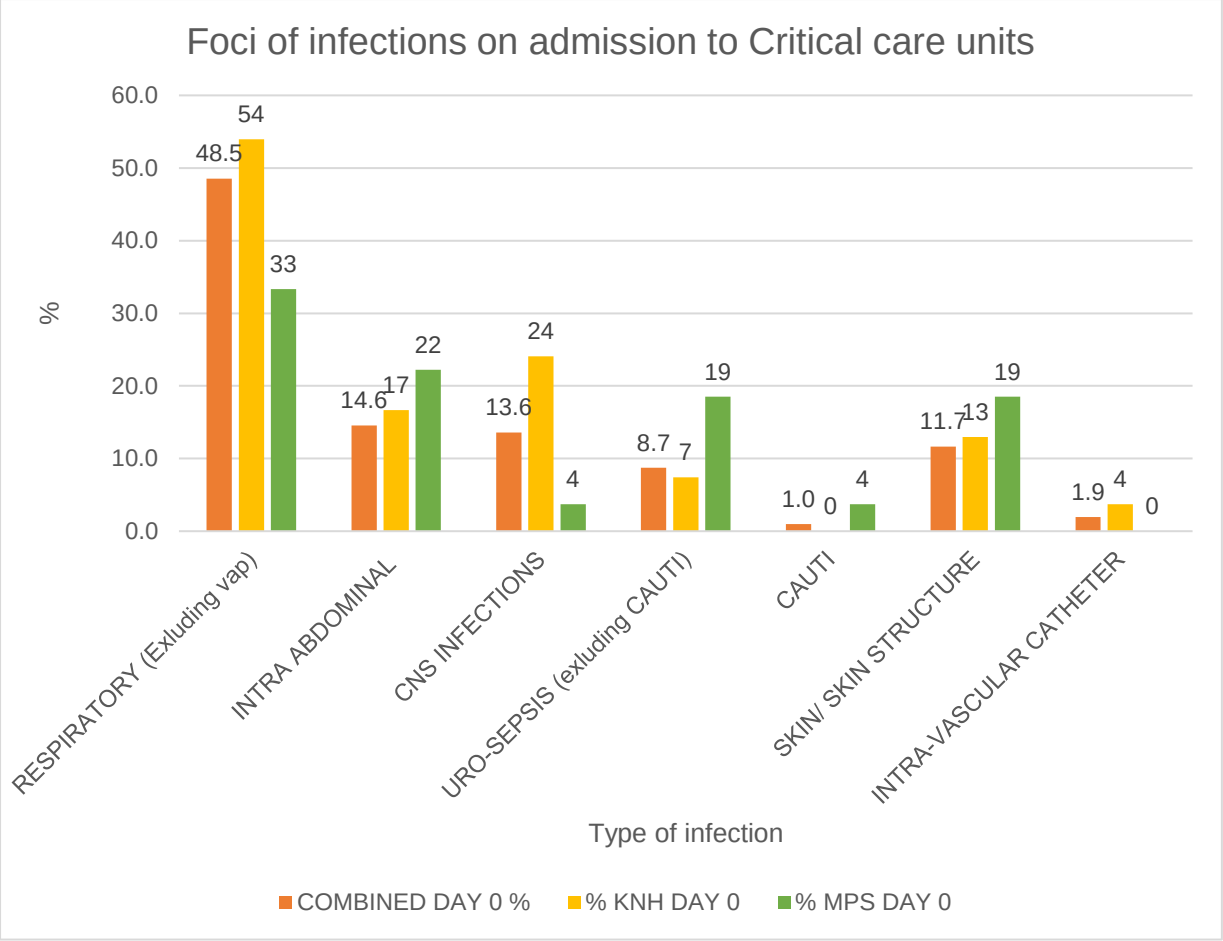

Figure 13: Bar chart illustrating the foci of prevalent infection on admission to critical care units at KNH and MPSH.

10.7 Foci of incident infections in Critical care units

Subjects were screened using the ISF definitions for development of incident infections. Among subjects in the combined sample, 66 subjects developed one or more infections. Among these subjects, 79%(n=52) had a singular focus of infection and 21% (n=14) had multiple foci computing a total of 80 foci of infection.

Foci of infection among incident infections acquired in the critical care units were CAUTI (33%), VAP (30%), intravascular catheter infections (16%), bloodstream infections (10%), skin and skin structure infections (8%) and non-ventilator respiratory infections (4%).

From the KNH sample cohort, 54 subjects developed one or more incident infections. Among these subjects, 85% (n=46) had a singular focus of infection and 15% (n=8) had multiple foci computing a total of 62 foci of infection. Foci of incident infections were CAUTI (31%), VAP

(34%), intravascular catheter associated infections (16%), skin and skin structure infections (6%), and non-ventilator respiratory infections (3%).

Among the MPSH sample cohort, 12 subjects developed one or more infections. Among these subjects, 50% (n=6) had a singular focus while 50% (n-6) had multiple foci computing a total of 18 foci of infection. Foci of incident infections were CAUTI (n=7), VAP (n=3), intravascular catheter associated infections (n=3), skin and skin structure infections (n=2), and non-ventilator respiratory infections (n=1). This is illustrated in table 14 and figure 15.

Table 13: Foci of CCU acquired infections among patients in critical care units

TYPE OF INFECTION	**COMBINED CCU ACQ**	**CCU ACQ. KNH**	**CCU ACQ.MPS**
	FREQUENCY (%)	**FREQUENCY (%)**	**FREQUENCY**
CAUTI	26 (33%)	19 (31%)	7
VAP	24 (30%)	21 (34%)	3
INTRA-VASCULAR CATHETER	13 (16%)	10 (16%)	3
BLOOD STREAM	8 (10%)	6 (10%)	2
SKIN/ SKIN STRUCTURE	6 (8%)	4 (6%)	2
RESPIRATORY (Excluding VAP)	3 (4%)	2 (3%)	1
TOTAL	80	62	18

CCU ACQ: Critical care unit acquired infection.

VAP: Ventilator associated pneumonia

CAUTI: Catheter associated urinary tract infection, CNS: Central nervous system

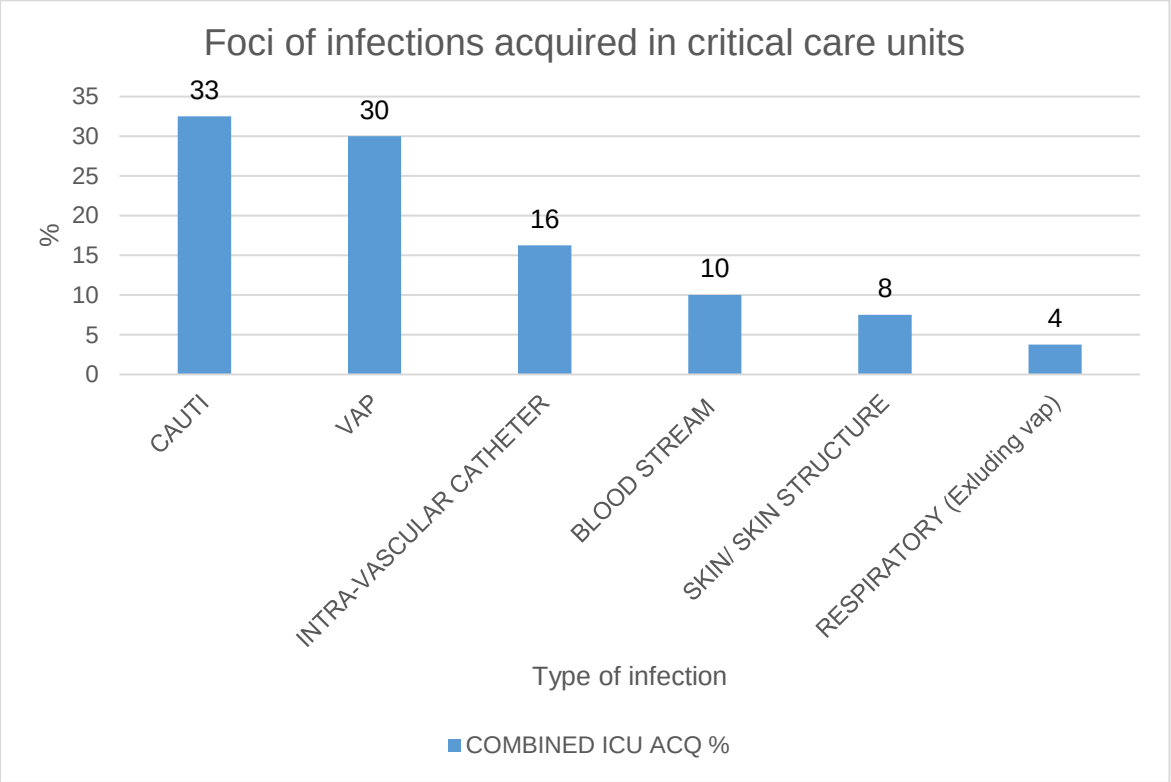

Figure 14: Bar chart showing the foci of CCU acquired infections in the combined sample cohort

10.8 Organisms isolated from microbial cultures

A total of 321 specimen cultures were analyzed from both hospitals, 62% from KNH and 38.0% from MP shah. Cultures taken from KNH were tracheal aspirates at 34.6%, urine at 34.6% and blood at 17.1%.

Cultures taken from MP Shah were blood at 35.2%, urine at 33.6% and pleural fluid at 5.7%. The culture positivity rate (all culture specimens) was 33.7% (n=67; 95%CI: 27.1-40.7) at KNH and 15.6% (n=19; 95%CI: 9.6-23.2) at MP. Shah. (See table 15)

Analysis of antimicrobial sensitivity patterns was done from the combined set of culture reports. Organisms isolated from all culture samples included *E. coli* at 19%, *K. Pneumoniae* at 15%, *S. Aureus* at 14% and *A. Baumanii* at 13%. (See Table 16 and Figure 16).

The 31 positive tracheal aspirates yielded *S. Aureus*, at 25%, *K. pneumoniae* at 22%, *A. Baumanii* at 19%, *E. Coli* at 13% and *Aeruginosa* at 9%. (See Table 22 and Figure 17)

Seventeen positive blood cultures yielded Coagulase negative *Staphylococci* with 6 isolates, *K. Pneumonia* with 3 isolates and *C.Albicans* with 2 isolates. (Table 18).

15 positive urine cultures yielded *E.coli* with 8 isolates, *A. Baumanii* with 3 isolates, *E.faecium* with 2 isolates, *E.Cloacae* and *P.aureginosa* with 1 isolate each. (Table 19)

A total of seven positive pus swabs were documented and the commonest organism isolated was *E.Coli* with 3 isolates. (Table 20)

Five positive sputum cultures were documented from which *K.Pneumoniae* with 2 isolates, was the commonest microorganism isolated.

CSF analysis yielded *C. neoformans* with 2 isolates, *M.Tuberculosis* with 1 isolate and *E.fecium* with 1 isolate.

Central venous catheter tip cultures yielded two isolates, *A. Baumanii* and *S. Aureus* while ascitic fluid cultures yielded *E.asburiae* as the single isolate.

Table 14: Numbers, types and proportions of culture specimens from among patients in critical care units

	COMBINED		KNH		MPSH	
SPECIMEN TYPE	**# SPECIMEN**	**POS. CULTURE N (%)**	**# SPECIMEN**	**POS. CULTURE N (%)**	**# SPECIMEN**	**POS. CULTURE N (%)**
TRACHEAL ASPIRATE	74	32 (50%)	69	31 (44%)	5	1
BLOOD	77	17 (22%)	34	14 (41%)	43	3 (7%)
CSF	20	4 (20%)	15	4	5	0
URINE	110	15	69	11	41	4
PUS SWAB	9	7	4	2	5	5
PLEURAL FLUID	7	1	0	0	7	1
ASCITIC FLUID	6	1	1	0	5	1
CATHETER TIP	6	2	1	1	5	1
SPUTUM	8	4	4	2	4	2
STOOL	2	1	0	0	2	1
VAGINAL SWAB	2	2	2	2	0	0
TOTAL	321	86	199	67	122	19

Pos. culture: Microbial cultures positive for growth

Table 15: Organisms isolated from microbial cultures from all samples documented.

ORGANISMS ISOLATED	**NUMBER 0F ISOLATES KNH +MP SHH**	**%**
Escherichia Coli	16	19
Klebsiella Pneumoniae	13	15
Staphylococcus Aureus	12	14
Acinetobacter. Baumanii	11	13
Coagulase Negative Staphylococci	10	12
Enterococcal Spp. (E. Fecalis, E. Cloacae, E. Fecium)	9	10
Pseudomonas Aeruginosa	4	5
Cryptococcus Neoformans	3	3
Mycobacterium Tuberculosis	3	3
Candida Species	2	2
Stenotrophomonas Maltophilia	1	1
Enterobacter Asburiae	1	1
Streptococcus Agalacticae	1	1
TOTAL	86	100

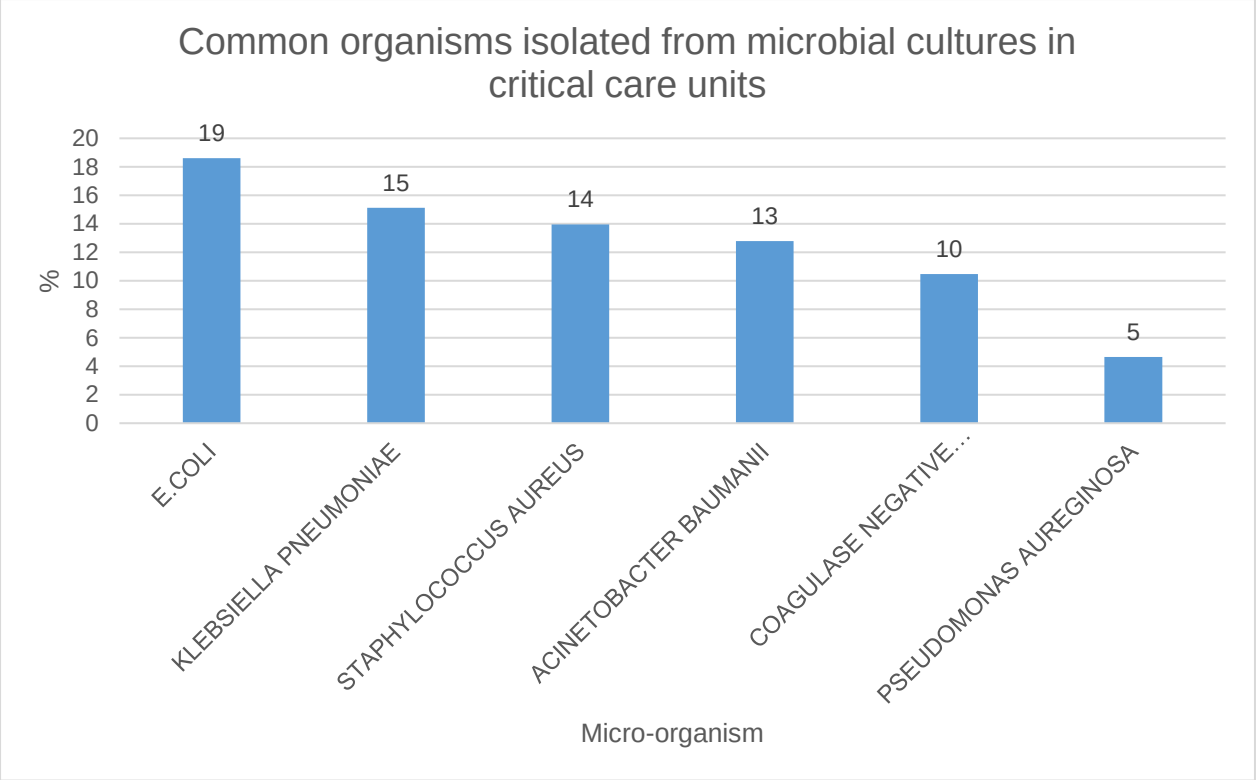

Figure 15: Bar chart illustrating common micro-organisms isolated from microbial culture samples in the critical care units.

Table 16: Organisms isolated from tracheal aspirate samples in the critical care units.

ORGANISM	**NO OF ISOLATES KNH +MPSH %**	**% KNH+MPSH**
Staphylococcus Aureus	8	25
Klebsiella Pneumoniae	7	22
Acinetobacter Baumanii	6	19
Escherichia .Coli	4	13
Pseudomonas Aureginosa	3	9
Coagulase Negative Staphylococci	1	3
Enterobacter Cloacae	1	3
Enterococcus Fecalis	1	3
Stenotrophomonas Maltophilia	1	3
TOTAL	32	100

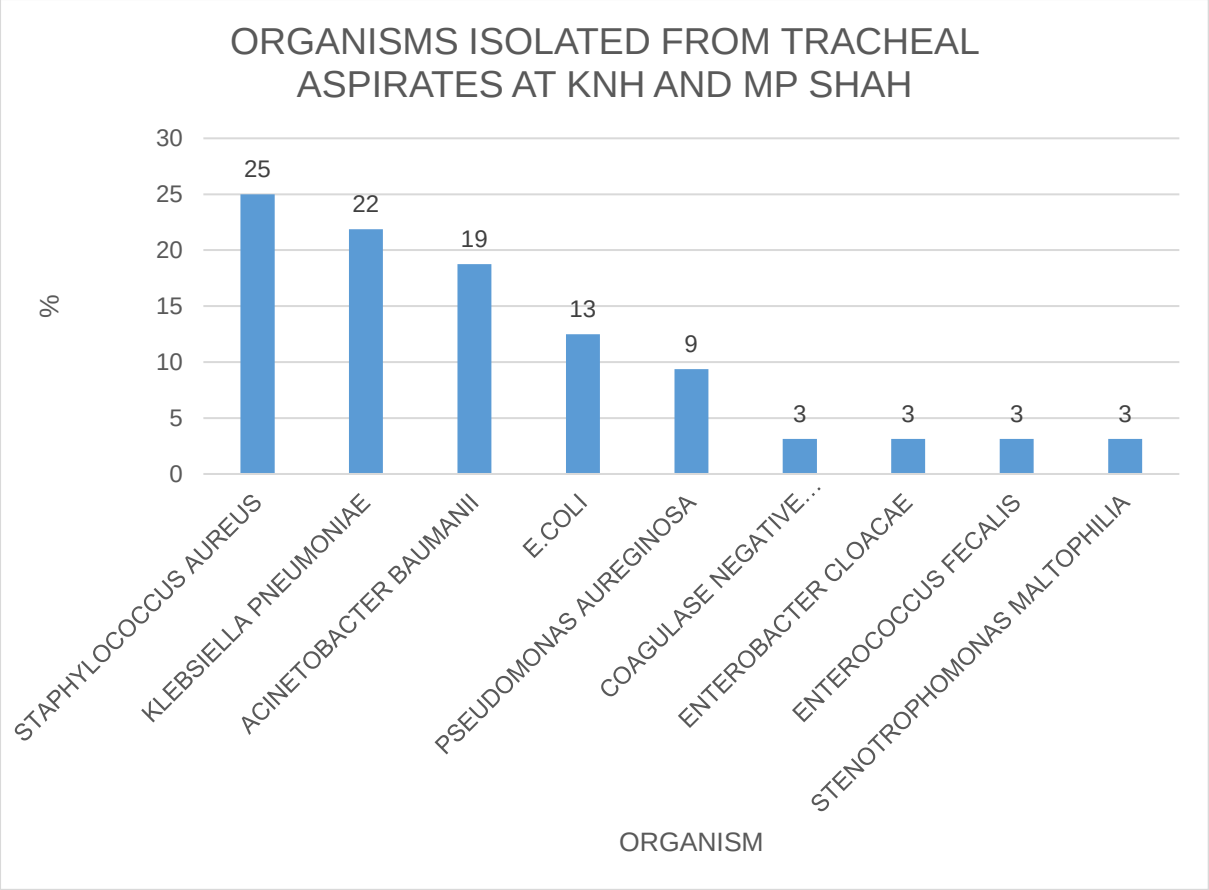

Figure 16: Bar chart illustrating micro-organisms isolated from tracheal aspirates in the critical care units.

Table 17: Organisms isolated from blood culture samples in the critical care units.

ORGANISM	**# KNH +MPSH**
Coagulase Negative Staphylococci	6
Klebsiella Pneumoniae	3
Candida Albicans	2
Staphylococcus Aureus	2
E. Coli	1
Enterococcus Fecalis	1
Skin Flora	1
Acinetobacter Baumanii	1
TOTAL	17.0

Table 18: Organisms isolated from urine culture specimens in the critical care units

ORGANISM	**NO OF ISOLATES KNH +MPSH**
E. Coli	8
Acinebacter Baumanii	3
Enterococcus Faecium	2
Enterobacter Cloacae	1
Pseudomonas Aureginosa	1
TOTAL	15

Table 19: Organisms isolated from pus swabs in the critical care units.

ORGANISM	**# KNH +MPSH**	**% KNH+MPSH**
E.Coli	3	42.9
Klebsiella Pneumoniae	2	28.6
Staphylococcus Saprophyticus	1	14.3
Streptococcus Agalacticae	1	14.3
TOTAL	7	100

10.9 Antimicrobial sensitivity and resistance patterns

Sensitivity and resistance patterns were analyzed for the micro-organisms with more than 10 isolates namely *E. coli, K. pneumoniae, S. aureus and A. baumanii.*

From the sixteen isolates of *E. coli* analyzed, fifteen were sensitive to Amikacin, twelve to Meropenem, nine to piperacillin/tazobactam and Nine to levofloxacin whereas eight of the isolates were resistant to Ceftazidime, six to Ceftriaxone, six to Amoxicillin/Clavulanic acid and five to Piperacillin/Tazobactam. (Table 21)

From thirteen isolates of *K. pneumoniae* analyzed, ten were sensitive to Meropenem and Amikacin, seven were sensitive to Cipro/Levofloxacin and six to Amoxicillin/Clavulanic acid. The resistance patterns obtained showed ten of the isolates were resistant to Ampicillin, eight to Cefepime and Ceftazidime, and five to Piperacillin/Tazobactam. (Table 22)

From eleven isolates of *S. aureus*, all eleven were sensitive to teicoplanin, nine were sensitive to linezolid, eight to levofloxacin and seven to clindamycin whereas eight of the isolates were resistant to benzylpenicillin, six to erythromycin and four to clindamycin. (Table 23)

Eleven isolates of *A. baumani* were analyzed of which eight were sensitive to colistin, four to ciprofloxacin, and three to meropenem whereas ten isolates were resistant to cefepime and ceftazidime, nine isolates were resistant to piperacillin/tazobactam and meropenem. (Table 24)

Table 20: Antimicrobial sensitivity and resistance patterns for isolates of E.Coli at KNH and MPSH critical care units.

SENSITIVITY PATTERNS	
ANTIMICROBIAL	**NUMBER (N=16)**
Amikacin	15
Meropenem	12
Piperacillin/Tazobactam	9
Cipro/Levofloxacin	9
Nitrofurantoin	6
Amoxy-Clav	4
RESISTANCE PATTERNS	
ANTIMICROBIAL	**NUMBER (N=16)**
Ceftazidime	8
Ceftriaxone	6
Amoxy-Clav	6
Ciprofloxacin	5
Ampicillin	5
Piperacillin/Tazobactam	5

Table 21: Antimicrobial sensitivity and resistance patterns for isolates of K. Pneumoniae at KNH and MP Shah critical care units.

SENSITIVITY PATTERNS	**NUMBER (n=14)**
ANTIMICROBIAL	
Meropenem	10
Amikacin	10
Amoxy-Clav	6
Ciprofloxacin/Levofloxacin	7
Cefepime	2
Ceftazidime	2
RESISTANCE PATTERNS	**NUMBER (n=14)**
Antimicrobial	
Ampicillin	10
Cefepime	8
Ceftazidime	8
Piperacillin/Tazobactam	5
Meropenem	3
Amikacin	2

Table 22: Antimicrobial sensitivity and resistance patterns for isolates of S. Aureus at KNH and MP Shah critical care units.

SENSITIVITY PATTERNS	
ANTIMICROBIAL	**NUMBER (N=11)**
Teicoplanin	11
Linezolid	9
Clindamycin	7
Tigecycline	6
Levofloxacin	8
RESISTANCE PATTERNS	**NUMBER (N=11)**
ANTIMICROBIAL	
Clindamycin	4
Benzylpenicillin	8
Erythromycin	6
Levofloxacin	2

Table 23: Antimicrobial sensitivity and resistance patterns for isolates of A. Baumanii at KNH and MP Shah critical care units.

SENSITIVITY PATTERNS	
ANTIMICROBIAL	**NUMBER (N=11)**
Colistin	8
Ciprofloxacin	4
Meropenem	3
Amikacin	1
RESISTANCE PATTERNS	**NUMBER (N=11)**
Cefepime	10
Ceftazidime	10
Piperacillin/Tazobactam	9
Meropenem	6
Ciprofloxacin	4

11.0 DISCUSSION

11.1: Prevalence, incidence and foci of infections, sepsis and septic shock

We set out to primarily determine the magnitude of infections and sepsis among CCU patients, determine 28-day Case fatality rates and characterize the microbial profile of infections.

Our study demographic consisted primarily of equally proportionate male and female patients between the ages of 30 and 59 years. Majority of the patients were admitted directly from home or transferred to the CCU from a hospital ward.

In this study, we observed a high prevalence of infection whereby 55% of all CCU patients had one or more prevalent infections while 35% and 14% of patients met the criteria for sepsis and septic shock respectively. Foci of prevalent infections were mainly respiratory, intra-abdominal and central nervous system infections.

The proportion of patients who developed one or more CCU acquired infections was as high as 41% whereas 25% and 11.6% developed sepsis and septic shock respectively. A significantly larger proportion of patients admitted to the parastatal hospital developed infections, sepsis and shock as compared to the private hospital The incidence density for infections was as high as 18.1 per 100 person days with the highest peak occurring on day 4 of admission whereas the peaks for sepsis and septic shock occurred on day 7 and 2 respectively. Foci of incident infections were mainly CAUTI's, VAP, and intravascular catheter related infections

The global prevalence rate of infections in critical care patients is approximately 51% while in Africa, the prevalence is estimated at 46% (30). Prevalence rates of sepsis globally are approximately 29%, whereas a Nigerian study demonstrated a prevalence as high as 66%.(62) Globally, the prevalence rate of septic shock is estimated at approximately 13.75%(63). According to data from the EPIC study, the foci of prevalent infections globally are mainly respiratory, intra-abdominal and bloodstream.(30)

Our study demonstrated prevalence rates of infections that were in line with global averages, however our prevalence rates of sepsis were significantly higher than the global average. In comparison with the EPIC study, our study found higher rates of CNS infections namely meningitis and encephalitis.

This data highlights a higher burden of sepsis in Kenyan CCU's compared to CCU's worldwide. Factors that contribute to this included a large proportion of patients that were

referrals from primary centers after clinical deterioration for higher level care especially in the KNH cohort, as well as a large proportion of retroviral disease co-infected patients.

Critical care patients have the highest incidence of infections among hospitalized patients with incidence rates of 21% globally whereas in Africa the incidence is as high as 35%. (63,64)The average global incidence density is 5.6 infections per 100 person days. The incidence of sepsis and septic shock worldwide is estimated at 11% and 5.8% respectively. Common foci of incident infections according to a large European audit were CAUTI's and VAP's. (47)
Our study demonstrated higher than average incidence rates of infections, sepsis and septic shock which can be attributed to high rates of invasive device related infections such as CAUTI's, VAP's and intravascular catheter associated infections that accounted for the bulk of incident infections. A high incidence of infections observed early on day 4 can be attributed to the presence of incubating infections among patients transferred from the ward. Development of new invasive device associated infections that were inserted on admission to the critical care units led to the peak incidence of sepsis on day 7. The highest rates of septic shock occurred very early on day 2 which can be explained by rapid deterioration to septic shock in subjects admitted with sepsis.

High numbers of CAUTI's have been linked to prolonged catheter stay with the risk increasing to almost 100% in 30 days.(16) Similarly prolonged periods of mechanical ventilation and poor endotracheal tube care have been directly associated with increased risk of VAP. (36). High rates of intravascular catheter infections have been linked to prolonged catheter use, poor septic techniques during fixation and use of multiple intravascular devices (51). On a larger scale, elevated infection rates have also been related to healthcare spending with higher infection rates observed in countries with lower percentages of GDP dedicated to healthcare spending.(63). Many hospital related factors including infection control practices and policies can also affect infection rates in ICU's. (65)

11.2: Case Fatality Rates

Our study found that case fatality rates among patients in the entire sample cohort were as high as 46% (significantly higher in the parastatal hospital) with CFS's in patients without infections, sepsis and septic shock at 27%, 47% and 59% respectively.

Patients in critical care units suffer from an average mortality of up to 9% in North American CCU's and 16% in African CCU's according to a recent audit. (5). Furthermore, patients with sepsis and septic shock suffer from even higher mortality rates of up to 35% and 40% respectively. Higher mortality rates have been reported in Lower income countries. According to prevalence studies, mortality rates for sepsis was 55% in Brazilian CCU's, and 64% in Indian CCU's. Mortality rates for septic shock were as high as 82% in Tunisia. (10)

Our study demonstrated a critical care unit CFR that was higher than global averages but in line with average CFRs from other lower income countries. Similarly, the CFRs among all patient subsets (no infections, sepsis and septic shock) were significantly higher than the global average but in line with data from other Lower income countries.
High mortality rates in our setting can be explained by a high prevalence of sepsis and septic shock on admission, as well as a high incidence of rates of CCU acquired infections which has been found to be an independent predictor of CCU mortality. (63). The ICON audit identified factors associated with high critical care mortality included advanced age, higher severity scores on admission as well as presence of multiple co-morbidities.(2) In our setting, although we had a relatively younger patient demographic, a large proportion of our patients had one or more co-morbidities which may have contributed to the high mortality rate observed. A high CFR in our patient population can also be explained by the large proportion of neurosurgical patients in the KNH cohort among which severe head injury accounted for more than one third. This also may have contributed to the high CFR among un-infected patients.

11.3: Microbial profile of organisms isolated

Our study also aimed to identify common causative organisms isolated and their antimicrobial susceptibility patterns. We discovered a high prevalence of Gram-negative bacteria namely *E. coli*, *K. pneumoniae* and *A. baumanii*. The most common Gram-positive isolate was *S. Aureus*. The majority of the *E. Coli* isolates were sensitive to aminoglycosides, carbapenems, and piperacillin/tazobactam. However, more than half were resistant to third generation cephalosporins, and more than a quarter were resistant to amoxicillin-clavulanic acid. The isolates of *K. Pneumoniae* were mainly sensitive to carbapenems, aminoglycosides and quinolones however almost all isolates were resistant to ampicillin, with significant resistance to cephalosporins. All isolates of *S. aureus* were sensitive to teicoplanin, with most sensitive to linezolid and levofloxacin, however the majority of isolates were resistant to benzylpenicillin

with some isolates resistant to oxacillin. Isolates of *A. baumanii* were almost universally resistant to third and fourth generation cephalosporin and showed extensive resistance to piperacillin/tazobactam and carbapenems as well.

According to large global studies. gram negative bacteria account for 62% of isolates in ICU's followed by Gram positive bacteria (47%) and fungal isolates (19%). (10,30) An African ICU study in Morocco similarly isolated *A.baumanii, E.Coli and K.Pneumoniae* in the majority of isolates.(55) A study in Uganda isolated K.*Pneumoniae, Acinetobacter and S.aureus* as the most frequently isolated bacteria.

In keeping with global data highlighted above, isolates in our study were predominantly gram-negative bacteria. The extensive resistance to third and fourth generation cephalosporins among all organisms suggest significant beta lactamase producing strains. The resistance patterns observed by K. *pneumoniae* suggest highly prevalent ESBL producing strains with emerging carabapenemase, DNA gyrase and aminoglycoside modifying enzyme producing strains. Extensive resistance to piperacillin tazobactam and carbapenems by Acinetobacter species suggests extended spectrum beta lactamase (ESBL) as well as carabapenemase producing strains. High prevalence rates of Acinetobacter are particularly significant as it is known to contaminate hospital water supplies. CCU practices such as flushing of nasogastric tubes with tap water and poor cleaning of ventilator circuits can lead to increased rates of Acinetobacter infection. (32)

11.4: Conclusion

The results from this study demonstrated higher than average prevalence rates of infections and sepsis among a relatively young critical care population with high rates of CCU acquired infections resulting in unacceptably high fatality rates. The data from this study sheds light on the current burden of infections and sepsis in critical care units, and highlights areas for potential interventions that aim to reduce the current morbidity and mortality rates.

11.5: Limitations

The lack of readily available lactate levels led to the utilization of the 2012 international definition of septic shock as opposed to the current definition which may have led to slight

over-estimation of prevalence and incidence rates of septic shock, however the rates for infection and sepsis remained unchanged.

The low positivity rate for antimicrobial cultures as well as the lack of sensitivity patterns for fungal culture isolates limited the sensitivity analysis for bacterial and fungal isolates.

11.6: Recommendations

Based on the results of this study, we make the following recommendations and highlight areas for potential improvement.

Early identification and aggressive management of infections and sepsis among patients in the ward to reduce the burden of prevalent infections in the CCU's.

Reinforcement of infection prevention programs in critical care units with emphasis on sterile techniques on insertion of invasive devices, early removal of urinary and intravascular catheters, thorough endotracheal tube care to prevent incident device related infections.

Antimicrobial resistance can be addressed by implementing routine microbial surveillance, creation of up-to-date hospital specific antibiograms and strengthening antimicrobial stewardship.

Further interventional studies also need to be done to audit the implementation of specific infection prevention measures in critical care units that may identify a discernible root cause of infections.

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13.0 APPENDICES

Appendix I: Patient Case Report Form

PATIENT CASE REPORT FORM

The data collected in this form is strictly confidential.

Section 1: Biodata

Patient Code
Date of admission (dd/mm/yyyy)
Sex (indicate M or F)
Age (years)
Telephone contact #1 Telephone contact #1
Next of kin contact Telephone contact 1: Telephone Contact 2:
Source of admission (tick as appropriate) Home ☐ Hospital Ward ☐ Other Hospital ☐
Patient Location KNH-I ☐ KNH- MICU 7 ☐ KNH- MICU 8 ☐ MPSH- I ☐ MPSH- H ☐
Date of Discharge from ICU/ Date of death (dd/mm/yyyy)

SECTION 2: CLINICAL ASSESSMENT DAY 0

Section 2a: Diagnostic Information

Diagnosis 1. 2.
Co-Morbidities (Tick all that apply) □ Liver cirrhosis □ Non-insulin dependent diabetes □ Insulin dependent diabetes □ Heart failure (NYHA III-IV) □ HIV infection □ Chronic renal failure □ Immunosuppressive therapy (including corticosteroids) □ Chemotherapy/radiotherapy □ Solid cancer If yes, Active □ Complete remission for < 5 years □ Complete remission > 5 years □ □ Hematologic cancer □ Known metastatic cancer
Has the patient had any surgical procedure in the last 30 days? If YES, Indicate the procedure below 1. 2. 3.

Core body temperature (min) _ _ . _ (max) _ _ . _ ° C
Fluid bolus received? YES ☐ NO ☐ IF yes, indicate the volume given: ……..(ml)
Interventions Invasive mechanical ventilation □ Yes □ No, If yes, Number of ventilator days: …….. Central venous catheter □ Yes □ No Pulmonary artery catheter □ Yes □ No Other cardiac output monitoring devices name(s)..... Hemodialysis catheter□ Yes □ No

Is the patient receiving antibiotics: □ Yes □ No If yes, list the antibiotics below 1. 2. 3. 4.
Serum Lactate (mmol): (if not done, indicate Not done)

Section 2b: Screening for infection: Refer to Appendix for specific definitions of infections.

Does the patient have an infection? Tick as appropriate
YES ☐ NO ☐ If YES, fill in the table below

	INFECTION #1	INFECTION #2	INFECTION #3
SITE			
MODE OF ACQUISITION	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community Acquired ☐ Hospital Acquired ☐ ICU acquired ☐

Section 2c: SOFA SCORE

Parameter Number	Parameter	Value	Score
1	Pa02/Fi02		
2	Platelet Count (*10^3 microlitres)		
3	Bilirubin (micromole/L)		
4	Glasgow Coma Score (x/15)		
5	Creatinine (micromole/L)		
	Urine Output		
6a	Mean Arterial Pressure		
	Inotropes/vasopressors Used. Indicate name and dose		
	Total Score	-	
	Baseline SOFA score.		

Section 2d: Microbial Culture and Antibiotic sensitivity reports

If results are pending, indicate "Pending" in the appropriate column

Type of Specimen	**Date collected**	**Date reported**	**Micro-organism grown**	**Sensitive to:**	**Resistant to:**

Section 2e: Patient categorization

Patient categorization (Tick the most appropriate)	1. NO INFECTION ☐ 2. INFECTION ☐ 3. SEPSIS ☐ 4. SEPTIC SHOCK ☐

SECTION 3: CLINICAL ASSESSMENT DAY 2

Section 3a: Diagnostic Information

Diagnosis 1. 2.
Has the patient had any surgical procedure in the last 30 days? If YES, Indicate the procedure below 1. 2. 3.

Core body temperature (min) _ _ . _ (max) _ _ . _ ° C
Fluid bolus received? YES ☐ NO ☐ IF yes, indicate the volume given: ……..(ml)
Interventions Invasive mechanical ventilation □ Yes □ No, If yes, Number of ventilator days: …….. Central venous catheter □ Yes □ No Pulmonary artery catheter □ Yes □ No Other cardiac output monitoring devices name(s)..... Hemodialysis catheter□ Yes □ No
Is the patient receiving antibiotics: □ Yes □ No If yes, list the antibiotics below 1. 2. 3. 4.
Serum Lactate (mmol): (if not done, indicate Not done)

Section 3b: Screening for infection: Refer to Appendix for specific definitions of infections.

Does the patient have an infection? Tick as appropriate
YES ☐ NO ☐ If YES, fill in the table below

	INFECTION #1	INFECTION #2	INFECTION #3
SITE			
MODE OF ACQUISITION	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community Acquired ☐ Hospital Acquired ☐ ICU acquired ☐

Section 3c: SOFA SCORE

Parameter Number	Parameter	Value	Score
1	Pa02/Fi02		
2	Platelet Count (*10^3 microlitres)		
3	Bilirubin (micromole/L)		
4	Glasgow Coma Score (x/15)		
5	Creatinine (micromole/L)		
	Urine Output		
6a	Mean Arterial Pressure		
	Inotropes/vasopressors Used. Indicate name and dose		
	Total Score	-	

Section 3d: Microbial Culture and Antibiotic sensitivity reports

If results are pending, indicate "Pending" in the appropriate column

Type of Specimen	Date collected	Date reported	Micro-organism grown	Sensitive to:	Resistant to:

Section 3e: Patient categorization

Patient categorization (Tick the most appropriate)	1. NO INFECTION ☐ 2. INFECTION ☐ 3. SEPSIS ☐ 4. SEPTIC SHOCK ☐

SECTION 4: CLINICAL ASSESSMENT DAY 4

Section 4a: Diagnostic Information

Diagnosis 1. 2.
Has the patient had any surgical procedure in the last 30 days? If YES, Indicate the procedure below 1. 2. 3.

Core body temperature (min) _ _ . _ (max) _ _ . _ ° C
Fluid bolus received? YES ☐ NO ☐ IF yes, indicate the volume given: ……..(ml)
Interventions Invasive mechanical ventilation □ Yes □ No, If yes, Number of ventilator days: …….. Tracheostomy □ Yes □ No Central venous catheter □ Yes □ No Pulmonary artery catheter □ Yes □ No Other cardiac output monitoring devices name(s)..... Hemodialysis catheter □ Yes □ No
Is the patient receiving antibiotics: □ Yes □ No If yes, list the antibiotics below 1. 2. 3. 4.
Serum Lactate (mmol): (if not done, indicate Not done)

Section 4b: Screening for infection: Refer to Appendix for specific definitions of infections.

Does the patient have an infection? Tick as appropriate
YES ☐ NO ☐ If YES, fill in the table below

	INFECTION #1	INFECTION #2	INFECTION #3
SITE			
MODE OF ACQUISITION	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community Acquired ☐ Hospital Acquired ☐ ICU acquired ☐

Section 4c: SOFA SCORE

Parameter Number	Parameter	Value	Score
1	Pa02/Fi02		
2	Platelet Count (*10^3 microlitres)		
3	Bilirubin (micromole/L)		
4	Glasgow Coma Score (x/15)		
5	Creatinine (micromole/L)		
	Urine Output		
6a	Mean Arterial Pressure		
	Inotropes/vasopressors Used. Indicate name and dose		
	Total Score	-	

Section 4d: Microbial Culture and Antibiotic sensitivity reports

If results are pending, indicate "Pending" in the appropriate column

Type of Specimen	**Date collected**	**Date reported**	**Micro-organism grown**	**Sensitive to:**	**Resistant to:**

Section 4e: Patient categorization

Patient categorization (Tick the most appropriate)	1. NO INFECTION ☐ 2. INFECTION ☐ 3. SEPSIS ☐ 4. SEPTIC SHOCK ☐

SECTION 5: CLINICAL ASSESSMENT DAY 7

Section 5a: Diagnostic Information

Diagnosis 1. 2.
Has the patient had any surgical procedure in the last 30 days? If YES, Indicate the procedure below 1. 2. 3.

Core body temperature (min) _ _ . _ (max) _ _ . _ ° C
Fluid bolus received? YES ☐ NO ☐ IF yes, indicate the volume given: ……..(ml)
Interventions Invasive mechanical ventilation □ Yes □ No, If yes, Number of ventilator days: …….. Tracheostomy □ Yes □ No Central venous catheter □ Yes □ No Pulmonary artery catheter □ Yes □ No Other cardiac output monitoring devices name(s)..... Hemodialysis catheter □ Yes □ No
Is the patient receiving antibiotics: □ Yes □ No If yes, list the antibiotics below 1. 2. 3. 4.
Serum Lactate (mmol): (if not done, indicate Not done)

Section 5b: Screening for infection: Refer to Appendix for specific definitions of infections.

Does the patient have an infection? Tick as appropriate
YES ☐ NO ☐ If YES, fill in the table below

	INFECTION #1	INFECTION #2	INFECTION #3
SITE			
MODE OF ACQUISITION	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community Acquired ☐ Hospital Acquired ☐ ICU acquired ☐

Section 5c: SOFA SCORE

Parameter Number	Parameter	Value	Score
1	Pa02/Fi02		
2	Platelet Count (*10^3 microlitres)		
3	Bilirubin (micromole/L)		
4	Glasgow Coma Score (x/15)		
5	Creatinine (micromole/L)		
	Urine Output		
6a	Mean Arterial Pressure		
	Inotropes/vasopressors Used. Indicate name and dose		
	Total Score	-	

Section 5d: Microbial Culture and Antibiotic sensitivity reports

If results are pending, indicate "Pending" in the appropriate column

Type of Specimen	Date collected	Date reported	Micro-organism grown	Sensitive to:	Resistant to:

Section 5e: Patient categorization

Patient categorization (Tick the most appropriate)	1. NO INFECTION ☐ 2. INFECTION ☐ 3. SEPSIS ☐ 4. SEPTIC SHOCK ☐

SECTION 6: CLINICAL ASSESSMENT DAY 10

Section 6a: Diagnostic Information

Diagnosis 1. 2.
Has the patient had any surgical procedure in the last 30 days? If YES, Indicate the procedure below 1. 2. 3.

Core body temperature (min) _ _ . _ (max) _ _ . _ ° C
Fluid bolus received? YES ☐ NO ☐ IF yes, indicate the volume given: ……..(ml)
Interventions Invasive mechanical ventilation □ Yes □ No, If yes, Number of ventilator days: …….. Tracheostomy □ Yes □ No Central venous catheter □ Yes □ No Pulmonary artery catheter □ Yes □ No Other cardiac output monitoring devices name(s)..... Hemodialysis catheter □ Yes □ No
Is the patient receiving antibiotics: □ Yes □ No If yes, list the antibiotics below 1. 2. 3. 4.
Serum Lactate (mmol): (if not done, indicate Not done)

Section 6b: Screening for infection: Refer to Appendix for specific definitions of infections.

Does the patient have an infection? Tick as appropriate
YES ☐ NO ☐ If YES, fill in the table below

	INFECTION #1	INFECTION #2	INFECTION #3
SITE			
MODE OF ACQUISITION	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community Acquired ☐ Hospital Acquired ☐ ICU acquired ☐

Section 6c: SOFA SCORE

Parameter Number	Parameter	Value	Score
1	Pa02/Fi02		
2	Platelet Count (*10^3 microlitres)		
3	Bilirubin (micromole/L)		
4	Glasgow Coma Score (x/15)		
5	Creatinine (micromole/L)		
	Urine Output		
6a	Mean Arterial Pressure		
	Inotropes/vasopressors Used. Indicate name and dose		
	Total Score	-	

Section 6d: Microbial Culture and Antibiotic sensitivity reports

If results are pending, indicate "Pending" in the appropriate column

Type of Specimen	Date collected	Date reported	Micro-organism grown	Sensitive to:	Resistant to:

Section 6e: Patient categorization

Patient categorization (Tick the most appropriate)	1. NO INFECTION ☐ 2. INFECTION ☐ 3. SEPSIS ☐ 4. SEPTIC SHOCK ☐

SECTION 7: CLINICAL ASSESSMENT DAY 14

Section 7a: Diagnostic Information

Diagnosis 1. 2.
Has the patient had any surgical procedure in the last 30 days? If YES, Indicate the procedure below 1. 2. 3.

Core body temperature (min) _ _ . _ (max) _ _ . _ ° C
Fluid bolus received? YES ☐ NO ☐ IF yes, indicate the volume given: ……..(ml)
Interventions Invasive mechanical ventilation □ Yes □ No, If yes, Number of ventilator days: …….. Tracheostomy □ Yes □ No Central venous catheter □ Yes □ No Pulmonary artery catheter □ Yes □ No Other cardiac output monitoring devices name(s)..... Hemodialysis catheter □ Yes □ No
Is the patient receiving antibiotics: □ Yes □ No If yes, list the antibiotics below 1. 2. 3. 4.
Serum Lactate (mmol): (if not done, indicate Not done)

Section 7b: Screening for infection: Refer to Appendix for specific definitions of infections.

Does the patient have an infection? Tick as appropriate
YES ☐ NO ☐ If YES, fill in the table below

	INFECTION #1	INFECTION #2	INFECTION #3
SITE			
MODE OF ACQUISITION	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community Acquired ☐ Hospital Acquired ☐ ICU acquired ☐

Section 7c: SOFA SCORE

Parameter Number	Parameter	Value	Score
1	Pa02/Fi02		
2	Platelet Count (*10^3 microlitres)		
3	Bilirubin (micromole/L)		
4	Glasgow Coma Score (x/15)		
5	Creatinine (micromole/L)		
	Urine Output		
6a	Mean Arterial Pressure		
	Inotropes/vasopressors Used. Indicate name and dose		
	Total Score	-	

Section 7d: Microbial Culture and Antibiotic sensitivity reports

If results are pending, indicate "Pending" in the appropriate column

Type of Specimen	Date collected	Date reported	Micro-organism grown	Sensitive to:	Resistant to:

Section 7e: Patient categorization

Patient categorization (Tick the most appropriate)	1. NO INFECTION ☐ 2. INFECTION ☐ 3. SEPSIS ☐ 4. SEPTIC SHOCK ☐

SECTION 8: CLINICAL ASSESSMENT DAY 21

Section 8a: Diagnostic Information

Diagnosis 1. 2.
Has the patient had any surgical procedure in the last 30 days? If YES, Indicate the procedure below 1. 2. 3.

Core body temperature (min) _ _ . _ (max) _ _ . _ ° C
Fluid bolus received? YES ☐ NO ☐ IF yes, indicate the volume given: ……..(ml)
Interventions Invasive mechanical ventilation □ Yes □ No, If yes, Number of ventilator days: …….. Tracheostomy □ Yes □ No Central venous catheter □ Yes □ No Pulmonary artery catheter □ Yes □ No Other cardiac output monitoring devices name(s)..... Hemodialysis catheter □ Yes □ No
Is the patient receiving antibiotics: □ Yes □ No If yes, list the antibiotics below 1. 2. 3. 4.
Serum Lactate (mmol): (if not done, indicate Not done)

Section 8b: Screening for infection: Refer to Appendix for specific definitions of infections.

Does the patient have an infection? Tick as appropriate
YES ☐ NO ☐ If YES, fill in the table below

	INFECTION #1	INFECTION #2	INFECTION #3
SITE			
MODE OF ACQUISITION	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community Acquired ☐ Hospital Acquired ☐ ICU acquired ☐

Section 8c: SOFA SCORE

Parameter Number	Parameter	Value	Score
1	Pa02/Fi02		
2	Platelet Count (*10^3 microlitres)		
3	Bilirubin (micromole/L)		
4	Glasgow Coma Score (x/15)		
5	Creatinine (micromole/L)		
	Urine Output		
6a	Mean Arterial Pressure		
	Inotropes/vasopressors Used. Indicate name and dose		
	Total Score	-	

Section 8d: Microbial Culture and Antibiotic sensitivity reports

If results are pending, indicate "Pending" in the appropriate column

Type of Specimen	Date collected	Date reported	Micro-organism grown	Sensitive to:	Resistant to:

Section 8e: Patient categorization

Patient categorization (Tick the most appropriate)	1. NO INFECTION ☐ 2. INFECTION ☐ 3. SEPSIS ☐ 4. SEPTIC SHOCK ☐

SECTION 9: CLINICAL ASSESSMENT DAY 28

Section 9a: Diagnostic Information

Diagnosis 1. 2.
Has the patient had any surgical procedure in the last 30 days? If YES, Indicate the procedure below 1. 2. 3.

Core body temperature (min) _ _ . _ (max) _ _ . _ ° C
Fluid bolus received? YES ☐ NO ☐ IF yes, indicate the volume given: ……..(ml)
Interventions Invasive mechanical ventilation □ Yes □ No, If yes, Number of ventilator days: …….. Tracheostomy □ Yes □ No Central venous catheter □ Yes □ No Pulmonary artery catheter □ Yes □ No Other cardiac output monitoring devices name(s)..... Hemodialysis catheter □ Yes □ No
Is the patient receiving antibiotics: □ Yes □ No If yes, list the antibiotics below 1. 2. 3. 4.
Serum Lactate (mmol): (if not done, indicate Not done)

Section 9b: Screening for infection: Refer to Appendix for specific definitions of infections.

Does the patient have an infection? Tick as appropriate
YES ☐ NO ☐ If YES, fill in the table below

	INFECTION #1	INFECTION #2	INFECTION #3
SITE			
MODE OF ACQUISITION	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community acquired ☐ Hospital Acquired ☐ ICU acquired ☐	Community Acquired ☐ Hospital Acquired ☐ ICU acquired ☐

Section 9c: SOFA SCORE

Parameter Number	Parameter	Value	Score
1	Pa02/Fi02		
2	Platelet Count (*10^3 microlitres)		
3	Bilirubin (micromole/L)		
4	Glasgow Coma Score (x/15)		
5	Creatinine (micromole/L)		
	Urine Output		
6a	Mean Arterial Pressure		
	Inotropes/vasopressors Used. Indicate name and dose		
	Total Score	-	

Section 9d: Microbial Culture and Antibiotic sensitivity reports

If results are pending, indicate "Pending" in the appropriate column

Type of Specimen	Date collected	Date reported	Micro-organism grown	Sensitive to:	Resistant to:

Section 9e: Patient categorization

Patient categorization (Tick the most appropriate)	1. NO INFECTION ☐ 2. INFECTION ☐ 3. SEPSIS ☐ 4. SEPTIC SHOCK ☐

Section 10: 28-day Mortality Assessment

Patient status at Day 28:

Alive ☐

Dead ☐

Appendix II: Estimating Fi02 from Various Oxygen Delivery Methods

Estimating FiO2 **Method**	**O2 flow (l/min)**	**Estimated FiO2 (%)**
Nasal cannula	1	24
2		28
3		32
4		36
5		40
6		44
Nasopharyngeal catheter	4	40
5		50
6		60
Face mask	5	40
6-7		50
7-8		60
>8		60
Face mask with reservoir	6	60
7		70
8		80
9		90
10		95

Appendix III: The SOFA score

SOFA score	1	2	3	4
Respiration PaO_2/FiO_2 (mm Hg)	<400	<300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation 10^{-3}/platelets/mm	<150	<100	<50	<50
Liver Bilirubin mg/dL (μM)	1.2–1.9 (20–32)	2–5.9 (33–101)	6–11.9 (102–204)	>12 (>204)
Cardiovascular Hypotension	MAp < 70 mm Hg	Dopamine ≤ 5[b] or dobutamine (any dose)	Dopamine > 5 or epinephrine ≤0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
CNS Glasgow Coma Score	13–14	10–12	6–9	<6
Renal Creatinine, mg/dL (μM) or urine output	1.2–1.9 (110–170)	2–3.4 (171–299)	3.5–4.9 (300–440) Or <500 mL/d	>5 (>440) or <200 mL/d

Abbreviations: CNS, central nervous system; SOFA, Sequential (Sepsis-Related) Organ Failure Assessment.
[a]Based on Vincent et al[53] and shows the potential values that contribute to the SOFA score.
[b]Catecholamine and adrenergic agents administered for at least 1 hour; doses in μg/kg/min.

Appendix IV: Data Collection Reference Sheet

INFECTION	DEFINITION
Pneumonia	Radiographic infiltrate plus the presence of fever and two of the following: Purulent sputum, cough, leukocytosis >11000, sp02 less than 90% on room air, or need for supplemental oxygen
Ventilator associated pneumonia	48 hours after endotracheal intubation plus the following criteria: chest radiograph that shows new or progressive infiltrates, consolidation, cavitation, or pleural effusion plus at least 1 of the following criteria: New onset of purulent sputum or change in character of sputum; organism cultured from blood; or isolation of a known etiologic agent from a specimen obtained by tracheal aspirate, bronchial brushing, or bronchoalveolar lavage, or biopsy
Urosepsis	Two of the following: Fever>38, urgency, frequency, dysuria or suprapubic tenderness PLUS any one of: i) Positive dipstick for leukocyte esterase and/or nitrate ii) Pyuria (>10 wbc/microliter or >3 wbc/hpf iii) Organisms seen on Gram stain iv) 2 urine cultures with repeated isolation of the same uropathogen of >10^2 cfu/ml v) 2 urine cultures with <10^5 of a single uropathogen in a patient on antimicrobial therapy
Blood-stream infection	**b)** Micro-organism not regarded as a common skin contaminant, (Diptheroids, Bacillus species, Propionibacterium, Coagulase negative Staphylococci, or micrococci) cultured from one or more blood cultures OR A common skin contaminant cultured from two or more blood cultures drawn on separate occasions. **c)** Infective Endocarditis: The Duke criteria will be used for the diagnosis of infective endocarditis. This is based on major and minor criteria. Infective endocarditis will be diagnosed in patients who meet the following clinical criteria: **i)** Two major criteria OR **ii)** One major and three minor criteria OR **iii)** Five minor criteria
Intravascular Catheter Related Infection	Presence of indwelling Central venous catheter in a patient with sepsis or septic shock and bacteremia based on either positive blood cultures and/or positive catheter tip cultures and/or clinical features such as erythema, cellulitis, pus from the catheter entry site.
Central Nervous System Infection	Bacterial Meningitis: Two out of four of: Headache, fever, neck stiffness, and altered level of consciousness (GCS<15) and CSF biochemistry findings showing glucose <2/3rd of blood glucose, elevated proteins >45g/dl and/or organisms on CSF microscopy (40). A positive CSF GeneXpert, CSF Ziehl Neelsen stain for

	acid-alcohol fast bacilli will be used to diagnose Tuberculous meningitis. A positive CSF Cryptococcal Antigen test will be used to diagnose Cryptococcal meningitis
	Encephalitis: Altered mental state >24 hours with three of the following: **iv)** Fever >38 C **v)** Generalized or partial seizures not fully attributable to a pre-existing seizure disorder **vi)** New onset of focal neurologic findings **vii)** CSF white cell count > 5/cubic mm **viii)** Neuroimaging suggestive of encephalitis **ix)** Abnormality on Electroencephalogram suggestive of encephalitis
Skin and Skin Structure Infections	Either one of the two criteria below: • Isolation by culture or Gram stain of a microorganism from a surgical wound or skin lesion that has drained pus, or from a skin aspirate or biopsy. • Clinical evidence such as spreading cutaneous erythema, blanching, or drainage of purulent material from a surgical wound PLUS either one of: o Fever >38.0°C o Leukocytosis >11000.
Intra-Abdominal Infections	Specific Definitions are below:
a) Primary Peritonitis	A compatible clinical illness with an inflammatory peritoneal fluid (>=500 leukocytes/mL) with/without a positive peritoneal fluid culture or Gram stain
b) Secondary Peritonitis	.Compatible clinical illness associated with free air in the abdomen on radiographic studies OR surgical confirmation of peritoneal inflammation following luminal perforation in the absence of positive cultures). 2.A Gram stain in the absence of a positive culture from the peritoneum with compatible clinical illness and evidence of perforation
c) Tertiary Peritonitis	Isolation of one or more nosocomial pathogens from peritoneal fluid or blood in an appropriate clinical situation, >48 hours after treatment for primary or secondary peritonitis. OR: Compatible clinical illness with documented secondary peritonitis with persistent peritoneal inflammation (>500 leukocytes/ml of fluid) in the absence of microbiologically confirmed microbial persistence in the peritoneal space.

d) Peritoneal Dialysis Catheter related peritonitis	Abnormal accumulation of inflammatory cells in the peritoneum (>=100 leukocytes/mL) with a predominance of neutrophils with/witout absence of Gram strain and culture evidence of infection in a patient receiving peritoneal dialysis.
e) Intra-abdominal abscess	Surgical or radiographic evidence of an abnormal fluid accumulation within the abdominal contents or surrounding structures with/without microbiologic or surgical confirmation.
f) Biliary tract infection	Patients with clinical evidence of biliary tract infection with surgical or radiographic evidence of suppurative complications with/without microbiologic verification, positive blood cultures, or a Gram stain evidence of active infection. In the presence of ascending cholangitis, a positive blood culture is sufficient. A positive culture from the biliary tract in the absence of clinical symptoms is not sufficient to make a diagnosis. Positive culture from a T-tube drainage from the common bile duct is not sufficient evidence to make a diagnosis of biliary tract infection if the tube has been in place for 24 hours.
g) Pancreatic Infection	Radiographic or direct surgical inspection with evidence suggestive of pancreatic abscess or other type of infection with/without microbiologic confirmation via percutaneous aspiration or biopsy.
h) Typhlitis	A compatible clinical presentation with radiographic evidence of bowel wall edema and/or gas and/or hemorrhagic necrosis within the bowel wall of the cecum with or without microbiologic or surgical confirmation.
i) Toxic Megacolon	A clinical presentation compatible with toxic megacolon and radiographic evidence of acute dilatation of the lumen of the large bowel 6 cm with or without microbiologic or pathologic confirmation.

Appendix V: Instructions for Filling the Form

INSTRUCTIONS FOR FILLING THIS FORM

All forms are to be filled out in full. The following instructions are with reference to specific fields in the form.

Section 1: Biodata

- **In Patient nr.:** Patient number provided by the coordinating center.
- **Date of admission:** The format day/month/year should be used
- **Age:** Patient's age (in years) on the day of the study
- **Admission source:** Only one choice is possible
- **Date of review:** The date the patient/file has been reviewed to collect data.
- **Follow up day:** Only one choice is possible
- **Patient Location:** Choose one.
    - KNH I: KNH Main ICU.
    - KNH MICU 7: KNH Medical ICU, 7th Floor
    - KNH MICU 8: KNH Medical ICU, 8th Floor
    - MPSH I: M.P. Shah ICU
    - MPSH H: M.P. Shah HDU

Section 2: Clinical Information

- **Primary diagnosis:** The main reason for admission to the ICU. Only one primary diagnosis should be entered.
- **Secondary diagnoses:** Defined as associated acute conditions on admission. Up to 3 secondary diagnoses are possible. If there are no relevant secondary diagnoses, please leave blank.
- Chronic diseases present prior to ICU admission. More than one can be chosen according to the following definitions:
    - **Metastatic cancer:** Metastases proven by surgery, computed tomography or magnetic resonance scan, or any other method.
    - **Hematologic cancer:** If yes, select appropriate box.
    - **HIV infection:** HIV positive patients.

- **Chronic renal failure:** Defined as either chronic dialysis dependent renal failure or history of chronic renal insufficiency with a serum creatinine > 3.6 g/dL (300 μmol/L).
- **Immunosuppression:** Administration within the 6 months prior to ICU admission of corticosteroid treatment (at least 0.3 mg/kg/day prednisolone for at least one month) or other immunosuppressant drugs, severe malnutrition, congenital immune-humoral or cellular immune deficiency state.

- **Min** refers to the lowest value and **max** to the highest value in the 24 hour-period. Both min and max values are required when indicated. If only one value has been recorded in the 24 hour-period, it should be noted in both fields (min & max).
- In patients without respiratory support, FiO2 can be estimated using the provided guidelines (listed separately at the end of this document).
- **PaO2 and FiO2** should be recorded simultaneously and the lowest value during the day is reported. In absence of respiratory support, use the provided guidelines to estimate the FiO2 and/or PaO2.
- If the patient stays for less than 24 hours (admitted or discharged during the day), the **urine output** should be estimated for the 24 hour period (for example, if the patient dies after 8 hours and had 500 ml *of* urine during his/her ICU stay, the urine output would be 1.5 L).
- Record the three components of the "estimated" **Glasgow coma score** (last pre-sedation GCS) and **the actual GCS on sedative/anesthetic agents**. If the patient cannot verbalize (e.g., endotracheal tube, tracheostomy, …) you should indicate for the verbal component what you feel the verbal response would be if the patient could verbalize.
- Infections should be defined as per the case definitions specified in the reference sheet.
- Hospital-acquired infections are those evident at least 48 hours after hospitalization. ICU acquired infections are defined as those occurring at least 24 hours following admission to the ICU.

Laboratory results, microbial culture reports

- Fill in the appropriate laboratory result values using the most recent values available.
- Fill in the antimicrobial culture data in the tables provided. Indicate “Pending” for reports that are not yet released.
- Calculate the current SOFA score using the information in the form.

- For patients who have been transferred from another ward or hospital use the baseline values that were taken on admission to give a baseline SOFA score. If the baseline score is not known, indicate ‘0’

Mortality Assessment

- Indicate vital status as ascertained through direct telephone contact.

Appendix VI: SOFA Score

System	Score 0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Appendix VII: Specific Definitions for Intra-abdominal Infections (Adapted from the International Consensus definitions on Infections. (16)

INFECTION	DEFINITION
Primary Peritonitis	A compatible clinical illness with an inflammatory peritoneal fluid (>=500 leukocytes/mL) with/without a positive peritoneal fluid culture or Gram stain
Secondary Peritonitis	1.Compatible clinical illness associated with free air in the abdomen on radiographic studies OR surgical confirmation of peritoneal inflammation following luminal perforation in the absence of positive cultures). 2.A Gram stain in the absence of a positive culture from the peritoneum with compatible clinical illness and evidence of perforation
Tertiary Peritonitis	Isolation of one or more nosocomial pathogens from peritoneal fluid or blood in an appropriate clinical situation, >48 hours after treatment for primary or secondary peritonitis. OR: Compatible clinical illness with documented secondary peritonitis with persistent peritoneal inflammation (>500 leukocytes/ml of fluid) in the absence of microbiologically confirmed microbial persistence in the peritoneal space.
Peritoneal Dialysis Catheter related peritonitis	Abnormal accumulation of inflammatory cells in the peritoneum (>=100 leukocytes/mL) with a predominance of neutrophils with/witout absence of Gram strain and culture evidence of infection in a patient receiving peritoneal dialysis.
Intra-abdominal abscess	Surgical or radiographic evidence of an abnormal fluid accumulation within the abdominal contents or surrounding structures with/without microbiologic or surgical confirmation.

Biliary tract infection	Patients with clinical evidence of biliary tract infection with surgical or radiographic evidence of suppurative complications with/without microbiologic verification, positive blood cultures, or a Gram stain evidence of active infection. In the presence of ascending cholangitis, a positive blood culture is sufficient. A positive culture from the biliary tract in the absence of clinical symptoms is not sufficient to make a diagnosis. Positive culture from a T-tube drainage from the common bile duct is not sufficient evidence to make a diagnosis of biliary tract infection if the tube has been in place for 24 hours.
Pancreatic Infection	Radiographic or direct surgical inspection with evidence suggestive of pancreatic abscess or other type of infection with/without microbiologic confirmation via percutaneous aspiration or biopsy.
Typhlitis	A compatible clinical presentation with radiographic evidence of bowel wall edema and/or gas and/or hemorrhagic necrosis within the bowel wall of the cecum with or without microbiologic or surgical confirmation.
Toxic Megacolon	A clinical presentation compatible with toxic megacolon and radiographic evidence of acute dilatation of the lumen of the large bowel 6 cm with or without microbiologic or pathologic confirmation.

Appendix VIII(a): Duke Criteria for Diagnosis of Infective Endocarditis

Diagnostic criteria for infective endocarditis. (66)

- Definite infective endocarditis
  - A. Pathologic criteria
    - (1) microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen, or
    - (2) pathologic lesions: vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis.
  - B. Clinical criteria*
    - (1) two major criteria, or
    - (2) one major and three minor criteria, or
    - (3) five minor criteria.
- Possible infective endocarditis
  Findings consistent with infective endocarditis that fall short of "definite" but are not "rejected."
- Rejected
  - (1) firm alternate diagnosis explaining evidence of infective endocarditis, or
  - (2) resolution of infective endocarditis syndrome with antibiotic therapy for ≤4 days, or
  - (3) no pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤4 days.

Appendix VIII(b): Definition of Terms for Diagnosis of Infective Endocarditis. (66)

- Major criteria:
  - (1) Positive blood culture for IE:
    - A. Typical microorganism consistent with IE from two separate blood cultures as noted below:
      - (i) viridans streptococci,* *Streptococcus bovis*, HACEK group, or
      - (ii) community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus, or
    - B. Microorganisms consistent with IE from persistently positive blood cultures defined as:
      - (i) at least two positive cultures of blood samples drawn >12 hours apart or
      - (ii) all of three or a majority of four or more separate cultures of blood (with first and last sample drawn at least 1 hour apart).
  - (2) Evidence of endocardial involvement
    - A. Positive echocardiogram for IE defined as:
      - (i) oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or
      - (ii) abscess, or
      - (iii) new partial dehiscence of prosthetic valve
    - B. New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)
- Minor criteria
  - (1) Predisposition: predisposing heart condition or intravenous drug use
  - (2) Fever: temperature, ≥38.0°C
  - (3) Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions
  - (4) Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
  - (5) Microbiological evidence: positive blood culture but does not meet a major criterion as noted in table 2* or serological evidence of active infection with organism consistent with IE
  - (6) Echocardiographic findings: consistent with IE but do not meet a major criterion as noted in table 2

Appendix IX (a): Patient Consent Form (English)

PATIENT CONSENT FORM

TITLE: PREVALENCE AND INCIDENXE OF SEPSIS IN PATIENTS ADMITTED TO INTENSIVE CARE UNITS AT KENYATTA NATIONAL HOSPITAL AND M.P. SHAH HOSPITAL.

Hi, I am Dr. Naveed Merali, a postgraduate student in Internal Medicine and I am conducting a research on sepsis in Intensive Care Unit's (ICU).

What does the study involve?

Sepsis is a state of inflammation in the body that has been caused by an infection. It is major cause of illness and mortality in ICU patients worldwide. Patients in ICU also tend to develop new infections easily that can be caused by resistant bacteria that is difficult to treat.

We currently do not have enough research on the types of infections in ICU patients, the numbers of patients that develop sepsis and the types of bacteria that cause it. This study aims to address these issues to obtain valuable data to treat our patients better.

If you agree to participate, clinical information and laboratory test results regarding your illness will be collected from your hospital file. No additional blood tests will be done that are not part of your routine care and you will not be required to pay to participate.

We will also need to contact you or your next of kin via telephone 28 days from the date of admission.

How do I benefit from the study?

As a patient or next of kin for a patient who in in the ICU, the data collected will help doctors understand your disease better, and help doctors treat infections better. The data collected will also inform doctors on better antibiotic choices for infections.

Are there any risks?

There are no risks involved in the study. Data will be collected from patient files and reports.

Do I have to take part?

Do I have to take part?

Taking part in this study is voluntary. You shall not be forced to participate in the study. Should you agree to take part you are given this information sheet to keep and was expected to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. You will still receive all treatment that you should get even without participating in the study.

How can I take part?

As a patient, you can sign this form at the place indicated. As the next of kin for a patient who is unable to sign for themselves, you can sign on their behalf. This allows us to enroll you into the study.

Confidentiality

Any data collected for this study will only be accessible to authorized persons. This will minimize accidental disclosure to any unauthorized personnel. Results will only be made available to the patient and his/her primary care provider. It is the responsibility of the principal investigator that patient confidentiality is maintained.

Thank you for taking the time to read this information sheet.

Patient Name	
Next of kin	
ID number	
Telephone Contact	
Signature	

Contact Details:

Primary Investigator:

Dr Naveed Merali. Tel: 0708847255, Naveed.merali@gamil.com

Supervisor:

Dr. Enoch Omonge. Tel: 0721562033, omongedr@yahoo.com

KNH-UON ERC:

Uonknh_erc@uonbi.ac.ke

Appendix IX (b): Patient Consent Form (Kiswahili)

PATIENT CONSENT FORM

TITLE: PREVALENCE AND INCIDENCE OF SEPSIS IN PATIENTS ADMITTED TO INTENSIVE CARE UNITS AT KENYATTA NATIONAL HOSPITAL AND M.P. SHAH HOSPITAL.

Jambo, mimi ni Dr. Naveed Merali, mwanafunzi wa shahada ya kwanza katika Tiba ya Ndani na ninafanya utafiti juu ya sepsis katika Kitengo ya Huduma ya Wakuu (ICU).

Je Utafiti unahusisha nini?

Sepsis ni hali ya uchochezi katika mwili ambayo imesababishwa na maambukizi. Ni sababu kubwa ya magonjwa na vifo kwa wagonjwa wa ICU ulimwenguni kote. Wagonjwa katika ICU pia huwa na maambukizo mapya kwa urahisi ambayo yanaweza kusababishwa na bakteria sugu ambayo ni ngumu kutibu.

Hivi sasa hatuna utafiti wa kutosha juu ya aina ya maambukizo kwa wagonjwa wa ICU, idadi ya wagonjwa ambao hutengeneza sepsis na aina za bakteria zinazosababisha. Utafiti huu unakusudia kushughulikia maswala haya kupata data muhimu ya kuwatibu wagonjwa wetu.

Ikiwa unakubali kushiriki, habari ya kliniki na matokeo ya mtihani wa maabara kuhusu ugonjwa wako yatakusanywa kutoka faili yako ya hospitali. Hakuna majaribio ya ziada ya damu yatafanywa ambayo sio sehemu ya utunzaji wako wa kawaida na hautalazimika kulipa ili kushiriki. Tutahitaji pia kuwasiliana na wewe au ndugu yako kupitia simu siku 28 tangu tarehe ya kuandikishwa.

Ninanufaikaje na masomo?

Kama mgonjwa au mtu wa ukoo kwa mgonjwa ambaye katika ICU, data iliyokusanywa itasaidia madaktari kuelewa ugonjwa wako vizuri, na kusaidia madaktari kutibu maambukizo bora. Takwimu zilizokusanywa pia zitafahamisha madaktari juu ya chaguo bora zaidi za antibiotic kwa maambukizo.

Kuna hatari yoyote?

Hakuna hatari zinazohusika katika utafiti. Takwimu zitakusanywa kutoka kwa faili za mgonjwa na ripoti.

Ni lazima nishiriki ?

Kushiriki katika utafiti huu ni kwa hiari. Hautalazimishwa kushiriki katika utafiti. Lazima kukubaliana na kushiriki wewe ni kupewa laha hii habari ya kuweka na alitarajiwa kuingia fomu ya ridhaa. Ukiamua kuchukua sehemu bado uko huru kujiondoa wakati wowote na bila

kutoa sababu. Bado utapokea matibabu yote ambayo unapaswa kupata hata bila kushiriki katika utafiti.

Ninawezaje kushiriki?

Kama mgonjwa, unaweza kusaini fomu hii katika sehemu iliyoonyeshwa. Kama ndugu wa jamaa kwa mgonjwa ambaye hayawezi kujisajili, unaweza kusaini kwa niaba yao.

Usiri

Data yoyote iliyokusanywa kwa utafiti huu itapatikana tu kwa watu walioidhinishwa. Hii itapunguza kufichuliwa kwa bahati mbaya kwa wafanyikazi yoyote wasio ruhusa. Matokeo yatapatikana tu kwa mgonjwa na mhudumu wake wa msingi. Ni ni jukumu la mpelelezi mkuu kwa mgonjwa siri imedumishwa.

Asante kwa kuchukua wakati wa kusoma karatasi hii ya habari.

Jina la mgonjwa	
Jamaa wa jamaa	
Nambari ya kitambulisho	
Nambari ya simu	
Sahihi	

Contact Details:

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