A SURVEY OF THE PRACTICE IN THE MANAGEMENT OF SEVERE SEPSIS AND SEPTSC SHOCK BY ANAESTHESIA PRACTITIONERS AT THE KENYATTA NATIONAL HOSPITAL CRITICAL CARE UNIT

A DISSERTATION PRESENTED IN PART FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF A MASTERS DEGREE IN ANAESTHESIA, UNIVERSITY OP MAI ROBS

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A SURVEY OF THE PRACTICE IN THE MANAGEMENT OF SEVERE SEPSIS AND SEPTIC SHOCK BY ANAESTHESIA PRACTITIONERS AT THE KENYATTA NATIONAL HOSPITAL CRITICAL CARE UNIT

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DECLARATION

I declare that this dissertation is my original work and has not been submitted for a degree award in any university.

RESEARCHER SIGNATURE DATE

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This dissertation has been submitted for the degree of Masters of Medicine in Anaesthesiology with my approval as a university supervisor.

SUPERVISOR SIGNATURE DATE

DEDICATION

Dedicated to my mother Mrs Margaret Mwai, for her tremendous support and encouragement.

ACKNOWLEDGEMENTS

I sincerely thank and acknowledge the following:

- Dr. J Muriithi, my supervisor for his guidance and supervision in writing this dissertation.
- Dr. T Chokwe for reviewing and refining this study.
- The KNH/UON Ethics and Research Committee for allowing this study to be conducted.
- Eric for his time and effort in data entry and database creation.
- All KNH anaesthesia practitioners for their enthusiastic response to the survey questionnaire.

TABLE OF CONTENTS

ABBREVIATIONS

SIRS - Systemic Inflammatory Response Syndrome

PCR - Polymerase Chain Reaction

ALI - Acute Lung Injury

ARDS- Acute Respiratory Distress Syndrome

GCS- Glasgow Coma Scale

INR- International Normalised Ratio

CCU- Critical Care Unit

LPS - Lipopolysaccharide

KNH- Kenyatta National Hospital

APC - Activated Protein C

DIC- Disseminated Intravascular Coagulation

CRP - C -reactive protein

NIBP - Non-invasive Blood Pressure

IABP- Intra-arterial Blood Pressure

SpO_2 - Oxygen saturation

PaO_2 - Partial pressure of oxygen

FiO_2 - Fraction of inspired oxygen

CVP - Central Venous Pressure

$ScVO_2$ - Central Venous Oxygen Saturation

LIST OF FIGURES AND TABLES

SUMMARY

Background

Severe sepsis and septic shock is a major contributor of morbidity and mortality worldwide. Kenyatta National Hospital is the main referral hospital with the largest critical care unit in Kenya. In 2009, severe sepsis and septic shock contributed 8% of admissions to the critical care unit, with a mortality of up to 70%.[1]

Objectives

There have been efforts worldwide aimed at reducing mortality from severe sepsis and septic shock. The objective of the study was to review the current management practices of patients with severe sepsis and septic shock by the anaesthesia and critical care practitioners, comparing it with the surviving sepsis campaign guidelines, and to identify the challenges faced in managing these patients.

Methodology

The study was a cross sectional descriptive survey of anaesthesia practitioners at the Kenyatta National Hospital Critical Care Unit. The study population included physician anaesthesiologists and senior post-graduate students in the anaesthesia program. Data was collected by use of a self administered questionnaire to the anaesthesia practitioners. Data collected was analyzed by use of Statistical Package for Social Sciences Version 17 and Microsoft Excel spreadsheet.

Results

Forty five anaesthesia practitioners were surveyed. 58% were consultant anaesthesiologists and 42% were part two post-graduate anaesthesia students. The lungs were stated as the most common site of infection leading to sepsis by 31% of respondents. 51% correctly indicated the lactic acid level above which would indicate tissue hypoxia in sepsis. The monitoring parameters which were ranked as the most important in sepsis by the respondents were CVP (93.3%), NIBP (91.1%), Foley catheter (91.1%) and oxygen saturation (88.9%). Over half the respondents used normal saline (91.1%), Ringers lactate (66.6%) and hemacael (61.0%) 'often' or 'always' for early fluid resuscitation. The four most cited resuscitation end points were urine output (93.3%), CVP (93.3%), peripheral perfusion (93.3%) and blood pressure (91.1%). Only 37.8% of the respondents felt that the target CVP in a mechanically ventilated patient

during initial fluid resuscitation should be 14cmH_20. 82.2% of the respondents would consider transfusion of packed red cells if the $Scv0_2$ of 70% is not achieved after fluid resuscitation to target CVP with all the respondents stating they would start an inotropic agent to further increase oxygen delivery if the $Scv0_2$ was still below the set goal. 24.4% of the respondents recommended dobutamine as the 1st inotropic agent of choice. 42.2% of the respondents would use a haemoglobin transfusion trigger of 7g/dl to administer a red blood cell transfusion. All the anaesthesia practitioners sampled would start empirical intravenous combination antibiotic therapy within the 1st hour of recognition of septic shock or severe sepsis. All recommended de-escalation to the most appropriate single therapy after susceptibility profile is known. The 1st choice vasopressor agent for correction of hypotension in septic shock is norepinephrine from the responses sampled. 64% of the respondents recommended a conservative fluid strategy for patients with established ALI/ARDS. Key challenges in patient care revealed many resource limitations with limited CCU bed space and delay in surgical intervention standing out.

Recommendations

KNH should come up with a protocol to guide in management of severe sepsis and septic shock. Continuous medical education to the members of the care team on the current recommended practice is needed.

1.0 INTRODUCTION AND LITERATURE REVIEW

Sepsis has been active as long as infectious agents have been present. Because bacteria predate humans, sepsis probably predates modern man.[5] Despite intense efforts, sepsis remains a serious clinical problem, accounting for thousands of deaths every year. Many studies done have shown that severe sepsis is a common, expensive, and frequently fatal condition, with as many deaths annually as those from acute myocardial infarction.[b] Indeed, sepsis mortality is based on 28-day survival, in contrast to most mortality studies, which are based on 5-year survival. Therefore, in addition to its high lethality, sepsis also accounts for a significant number of years of life lost.

Two major consensus conferences have defined sepsis. The first, in 1992, put forth the concept of the Systemic Inflammatory Response Syndrome (SIRS), recognizing that lethally altered pathophysiology could be present without positive blood cultures.[2]

The 2001 International Sepsis Definitions Conference modified the model of SIRS and developed an expanded view of sepsis.[3] This conference developed the concept of a staging system for sepsis based on four separate characteristics designated by the acronym PIRO. P stands for the predisposition, indicating pre-existing co-morbid conditions that would reduce survival. I is the insult or infection, which reflects the clinical knowledge that some pathogenic organisms are more lethal than others. R represents the response to the infectious challenge, including the development of SIRS. The last letter O stands for organ dysfunction and includes organ failure as well as the failure of a system such as the coagulation system.

EPIDEMIOLOGY

From medical records review at KNH, severe sepsis and septic shock patients represented about 0.03 *% of* all admissions to the hospital in 2009. Of these patients, about 70% were admitted to the critical care unit with the mortality rate being 70%.[1]

Angus and coworkers [3] analyzed more than 6 million hospital discharge records from seven states in the USA and estimated that 751,000 cases of severe sepsis occur annually, resulting in 215,000 deaths, with a mortality rate of 28.6% and leading to average costs per case of US$22,100.

Another, international study conducted by Alberti and colleagues [9] examined 14,364 patients in six European countries, Canada and Israel, with more than 4500 documented infectious episodes either on ICU admission or during prolonged hospital stay. The authors found the combination of an infection at the time of ICU admission and subsequent hospital-acquired infections to be associated with a particularly devastating outcome, ranging from a crude hospital mortality rate of 16.9% for noninfected patients to 53.6% for patients who had repeated courses of infection while in the ICU.[9]

The therapeutic strategies and outcome of severe sepsis and septic shock do vary from country to country and even between different ICUs in a country. This will depend among other things on the availability of resources for management.

In 2002, the European Society of Intensive Care Medicine launched a survey on the incidence of sepsis and septic shock based on infection, inflammatory response and organ dysfunction in ICU patients (the Sepsis Occurrence in the Acutely III Patients [SOAP] study) that addressed various aetiologic, diagnostic, therapeutic and prognostic issues in this population[10]. This cohort, multicentre, observational study involved patients from 198 ICUs in 24 countries who were followed until death, hospital discharge or up to 60 days. The study revealed that there are large differences in diagnostic and therapeutic standards between the different countries as well as between ICUs in a particular country. The incidence of early cardiovascular failure and the widely ranging strategies employed for mechanical ventilation make it clear that recently

evaluated strategies, namely early goal-directed therapy to stabilize haemodynamics ' and use of low tidal volumes in mechanical ventilation,[11] are not yet routinely applied by intensivists.

Just like in any other discipline in medicine, compliance with new, evaluated strategies is a major problem in intensive care. Therefore, further education and quality assurance activities are crucial. It has been demonstrated that merely the participation of intensivists in clinical trials that were designed to measure the compliance of ICU physicians with guidelines before and after a defined time period was able to improve the quality of care.[1?]

PATHOPHYSIOLOGY

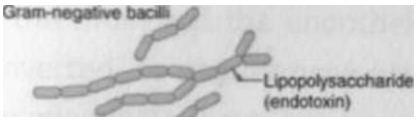
Inflammatory Cascade

Severe sepsis can occur as a result of infection at any body site, including the lungs, abdomen, skin or soft tissue, or urinary tract and as a result of a primary blood stream infection, such as in meningococcemia. Bacteria are the pathogens most commonly associated with the development of sepsis, although fungi, viruses, and parasites can cause sepsis.

The pathophysiology of sepsis can be initiated by the outer membrane component of gram-negative organisms or gram-positive organisms, as well as fungal, viral, and parasitic components. Signaling by these mediators occurs via a family of transmembrane receptors known as Toll-like receptors. Within the monocyte, nuclear factor-KB (NF-KB), is activated, which leads to the production of proinflammatory cytokines, tumor necrosis factor a (TNF-a), and interleukin 1 (IL-1).

TNF-a and IL-1 lead to the production of toxic downstream mediators, including prostaglandins, leukotrienes, platelet-activating factor, and phospholipase A2, damaging the endothelial lining, leading to increased capillary leakage.[1"] Furthermore, these cytokines lead to the production of adhesion molecules on endothelial cells and neutrophils with further endothelial injury through the release of the neutrophil components. Finally,

activated neutrophils release nitric oxide, a potent vasodilator that leads to septic shock.



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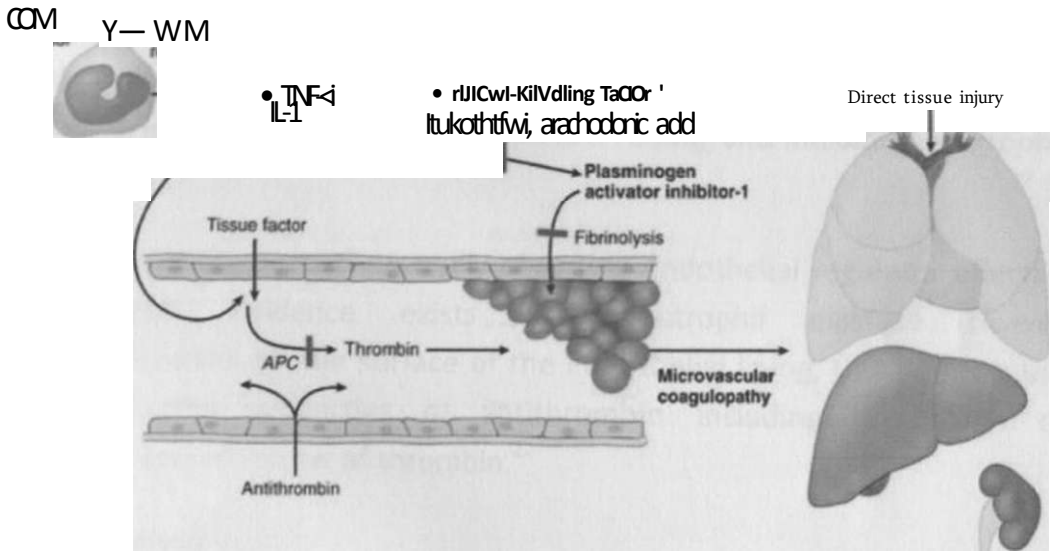


Link Between Inflammation and Coagulation

IL-1 and TNF-a also have direct effects on the endothelial surface. As a result of these inflammatory cytokines, tissue factor, the first step in the extrinsic pathway of coagulation, is expressed on the surfaces of the endothelium and of monocytes leading to the production of thrombin. Thrombin results in fibrin clots in the microvasculature, a sequela most easily recognized in meningococcal septic shock with purpura fulminans. IL-1 and TNF-a also lead to the production of plasminogen activator inhibitor-1, a potent inhibitor of fibrinolysis.[15]

Proinflammatory cytokines also disrupt the body's naturally occurring modulators of coagulation and inflammation, activated protein C (APC) and antithrombin. Protein C circulates as an inactive zymogen but, in the presence of thrombin and the endothelial surface-bound protein thrombomodulin, is converted to the enzyme-activated protein C. Studies have shown that proinflammatory cytokines can shear thrombomodulin from the endothelial surface as well as lead to downregulation of this molecule, thus preventing the activation of protein C.[10] APC and its cofactor protein S turn off thrombin production by cleaving factors Va and Villa. APC also restores fibrinolytic potential by inhibiting plasminogen activator inhibitor-l.[]/ [18] In vitro studies have revealed that APC has direct anti-inflammatory properties, including inhibiting the production of proinflammatory cytokines by LPS-stimulated monocytes, inhibiting leukocyte adhesion and rolling, and inhibiting neutrophil accumulation.[19 21]

Antithrombin is the second naturally occurring endothelial regulator affected during sepsis. Evidence exists that neutrophil elastase cleaves glycosaminoglycans off the surface of the endothelial lining, thus limiting the anti-inflammatory properties of antithrombin including production of prostacyclin and inhibition of thrombin.[22]

Immunoparalysis

CD4 lymphocytes play a key role in the inflammatory response seen in sepsis. Early in the sepsis process, these cells assume a TH1 phenotype, where they produce large amounts of the proinflammatory mediators, including interferon gamma, TNF-a, and IL-2. CD4 lymphocytes may evolve over time to a Th2 phenotype, whereby the CD4 lymphocytes produce anti-inflammatory cytokines, including IL-10, IL-4, and IL-13. This is often driven by the release of stress hormones, such as catecholamines and corticosteroids. These cytokines dampen the immune response and can lead to the deactivation of monocytes. Additionally, TNF released early can cause apoptosis of lymphocytes in the gut, leading to further immunosuppression.[23]

Severe Sepsis: The Final Common Pathway

As a result of the vicious cycle of inflammation and coagulation, cardiovascular insufficiency and multiple organ failure occur, and often lead to death. Cardiovascular insufficiency can occur at the level of the myocardium as a result of the myocardial depressant effects of TNF or at the level of the vessel, caused by vasodilation and capillary leak.[24]

Signs and symptoms

Clinical signs that may lead the physician to consider sepsis in the differential diagnosis include fever or hypothermia, unexplained tachycardia, unexplained tachypnea, signs of peripheral vasodilation, unexplained shock, and unexplained mental status changes. Hemodynamic measurements that suggest septic shock are an increased cardiac output, with a low systemic vascular resistance. Abnormalities of the complete blood count (CBC), laboratory test results, clotting factors, and acute-phase reactants might indicate sepsis (Table 1).

Table 1: Laboratory Indicators of Sepsis

Laboratory Test	Findings	Comments
White blood cell count	Leukocytosis or leukopenia	Endotoxemia may cause early leukopenia
Platelet count	Thrombocytosis or thrombocytopenia	High value early may be seen as acute-phase response; low platelet counts seen in overt DIC
Coagulation cascade	Protein C deficiency; antithrombin deficiency; elevated D-dimer level; prolonged PT and PTT	Abnormalities can be observed before onset of organ failure and without frank bleeding.
Creatinine level	Elevated from baseline	Doubling-indicates acute renal

		injury
Lactic acid level	Lactic acid > 4 mmol/L (36 mg/dL)	Indicates tissue hypoxia
Liver enzyme levels	Elevated alkaline phosphatase, AST, ALT, bilirubin levels	Indicates acute hepatocellular injury caused by hypoperfusion
Serum phosphate level	Hypophosphatemia	Inversely correlated with proinflammatory cytokine levels
C-reactive protein (CRP) level	Elevated	Acute-phase response
Procalcitonin level	Elevated	Differentiates infectious SIRS from noninfectious SIRS

ALT, alanine aminotransferase; AST, aspartate transaminase; DIC, disseminated intravascular coagulation; PT, prothrombin time; PTT, partial thromboplastin time; SIRS, systemic inflammatory response syndrome.

Conditions other than sepsis can produce a systemic inflammatory response and organ dysfunction. Noninfectious illnesses that should be considered in the differential diagnosis include tissue injury caused by trauma, hematoma, venous thrombosis, myocardial or pulmonary infarcts, transplant rejection, pancreatitis, hyperthyroidism, addisonian crisis, drug or blood product reaction, malignancies, and central nervous system hemorrhages.[25.]

DIAGNOSIS

The diagnosis of severe sepsis requires the presence of a presumed or known site of infection, evidence of a systemic inflammatory response, and an acute sepsis-associated organ dysfunction.

A presumed or known site of infection can be indicated by a purulent sputum or respiratory sample, or chest radiograph with new infiltrates not explained by a noninfectious process, spillage of bowel contents noted during an operation, radiographic or physical examination evidence of an infected collection, white blood cells in a normally sterile body fluid or a positive blood culture

Evidence of a systemic inflammatory response is usually indicated by at least two of the following: fever or hypothermia, tachypnea, tachycardia and white blood cell count of 12,000 cells/mm^3 or higher, 4,000 cells/mm^3 or less, or more than 10% bands on differential

Cardiovascular dysfunction is present when the mean arterial pressure is 60 mm Hg or lower, or when there is need for vasopressors to maintain this blood pressure in the presence of adequate intravascular volume or after an adequate fluid challenge has been given.

A diagnosis of respiratory organ failure is made when the arterial oxygen pressure-to-fraction of inspired oxygen ratio is less than 250 in the absence of pneumonia or is less than 200 in the presence of pneumonia.

Renal dysfunction is present when the urine output is less than 0.5 mL/kg/hr for 2 hours in the presence of adequate intravascular volume or after an adequate fluid challenge. Doubling of the serum creatinine level is also diagnostic.

Hematologic dysfunction is present when there is thrombocytopenia with less than 80,000 platelets/mm^3, or 50% decrease from baseline during the acute illness.

TREATMENT

Treatment of severe sepsis and septic shock rests on timely antibiotic therapy, surgical drainage of infected fluid collections, fluid management and appropriate support for organ dysfunction.

Appropriate Antimicrobial Treatment

Many clinical studies have demonstrated a twofold increase in mortality caused by sepsis when inappropriate antimicrobial therapy is given. More recent animal and human studies have demonstrated an incremental but statistically significant increase in mortality with each hour delay in the administration of appropriate antibiotic therapy from the onset of septic shock.''' When the clinician encounters a patient with severe sepsis, the site of infection and causative organism(s) often are unknown. Empirical antibiotics should be given in these cases. Appropriate empirical antimicrobial therapy should be guided by the knowledge of the most common sites of infection and the most common infecting organisms. A clinical trial of patients with severe sepsis has revealed that the lungs are the most common sites of infection, followed by the abdomen and urinary tract.'[8] In terms of pathogen type, gram-positive organisms cause sepsis slightly more often than gram-negative organisms with fungal organisms accounting for approximately 6% of cases.[13] The most common gram-positive organisms are *Staphylococcus aureus* and *Streptococcus pneumoniae,* and the most common gram-negative organisms are *Escherichia coli, Klebsiella* spp., *Pseudomonas* spp., and *Enterobacter* spp.[28] Samples for blood cultures should be taken from a percutaneous site and from any intravascular catheters. Samples for Gram staining and culture should be taken from suspected sites of infection. Combination empirical therapy should not be administered for more than three days.[29] De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known. Table 2 indicates appropriate empirical antibiotic choices by site of infection.

Table 2: Empirical Antimicrobial Therapy for Major Sites of Sepsis

Site of Infection	Microorganisms	Therapeutic Choices
Community-acquired pneumonia	*Streptococcus pneumoniae, Haemophilus influenzae, Legionella pneumophila, Mycoplasma pneumoniae*	Third-generation cephalosporin with macrolide or respiratory quinolone
Early hospital-acquired pneumonia (<5 days)	5. *pneumoniae, H. influenzae, L. pneumophila, M.* pneumonia; nonresistant gram-negative rods	Ceftriaxone, respiratory quinolone or ampicillin-sulbactam, or ertapenem
Late hospital-acquired pneumonia	*Pseudomonas aeruginosa, Klebsiella spp., Acinetobacter* spp., methicillin resistant *Staphylococcus aureus*	Antipseudomonal cephalosporin or carbapenem, or antipseudomonal beta-lactam or beta-lactamase inhibitor, *plus* linezolid or vancomycin
Intra-abdominal infections	Enteric gram-negative rods and anaerobes	Third-generation cephalosporin with metronidazole, or beta-lactam or beta-lactamase inhibitor, or carbapenem or moxifloxacin
Urinary tract infections	Gram-negative rods; *Enterococcus* spp.	Extended-spectrum beta-lactam or aztreonam, with or without an aminoglycoside; ampicillin or vancomycin if *Enterococcus* is present

Empirical antifungal therapy should be given to patients at high risk for fungemia. High-risk patients include those who have had prior colonization with *Candida* at two or more sites, those being treated with more than two different antibiotics, those who have taken antibiotics for more than 14 days, those who have had prior placement of a Hickman catheter, and those who have undergone prior hemodialysis.[30]

Source Control of Infection

Adequate source control of infection is as important as appropriate antimicrobial therapy in the treatment of a patient with severe sepsis. Source control of infection includes removal of infected foreign bodies, such as urinary catheters, intravascular catheters, peritoneal dialysis cannulas, prosthetic joints, vascular grafts, and mechanical valves. Incision and drainage of cutaneous abscesses as well as open or percutaneous drainage of intra-abdominal abscesses also fall under the principle of adequate source control of infection. " For patients with necrotizing fasciitis, mortality and extent of tissue loss are directly related to the rapidity of surgical intervention.

Optimizing Tissue Oxygenation

Optimizing the delivery of oxygen to critical organs is an urgent priority in the treatment of severe sepsis. The inability to meet tissue oxygen demand can be determined at the time of a patient's presentation to the emergency department by the presence of lactic acidosis that is when serum lactic acid level >4 mmol/L or 36 mg/dL. In this setting, the use of early goal-directed therapy (EGDT) to achieve a central venous oxygen saturation of 70% or higher has been shown to reduce mortality as well as hospital resources. EGDT is accomplished by first placing a central venous catheter to monitor the central venous oxygen saturation. Crystalloid boluses of 500 mL are given every 30 minutes to reach a central venous pressure (CVP) of 8 to 12 mm Hg. Currently, central venous pressure is the most readily obtainable target for fluid resuscitation."'[33] If the mean arterial pressure (MAP) is still below 65 mm Hg, vasopressor agents are added. If after these maneuvers the central venous oxygen saturation remains below 70%, red blood cells are transfused to reach

a hematocrit of 30%. If the target is still not reached, dobutamine is then administered.[3,1]

Fluid Resuscitation

The best type of fluid replacement and optimal volume of resuscitation in the setting of severe sepsis have been heavily debated but studies have provided guidance to the clinician. Many studies done have revealed no mortality advantage with the use of colloids compared with the use of crystalloids.[35,36] However, administration of hydroxyethyl starch may increase the risk of acute renal failure in patients with sepsis.[3/] In a clinical trial of patients with acute lung injury, the use of conservative fluid strategy was associated with a fewer number of ICU and ventilator days.[38] The preponderance of data would suggest that aggressive fluid management be done in the acute phase of sepsis, followed by a more conservative phase in the following few days.

Vasopressor Treatment

Dopamine and norepinephrine are the first-line agents for the treatment of septic shock. Dopamine increases cardiac index and systemic vascular resistance, whereas norepinephrine is a potent vasoconstrictor with few cardiac effects. Norepinephrine demonstrates a greater reversal of hypotension and lower mortality without suppressing the hypothalamic-pituitary axis.[39] Second-line agents for the treatment of septic shock include epinephrine and phenylephrine whose use is hampered by both drugs' negative effects on splanchnic blood flow.[40] Vasopressin on the other hand has become the agent of choice in cases of septic shock refractory to dopamine, norepinephrine, or both.[41,42]

Low-Dose Corticosteroid Treatment for Septic Shock

Corticosteroids have long been considered to be of potential use in the treatment of severe sepsis because of their anti-inflammatory properties and beneficial effects on vascular tone. Clinical trials of high-dose, short-course corticosteroids have not demonstrated benefits in mortality in patients with severe sepsis. However, trials of long-course, low-dose corticosteroids (<200 mg/day of hydrocortisone for >5 days) have demonstrated a shorter

time to shock reversal and improved mortality compared with placebo.[43] [45] Current clinical evidence would suggest treating only patients with shock refractory to vasopressors with low-dose, long-course corticosteroid therapy. Results of an ACTH test are not necessary to determine which patients should be treated.[46,47]

Recombinant Human Activated Protein C

Activated protein C is a molecule with anti-inflammatory, antithrombotic, and profibrinolytic properties. Recombinant human activated protein C (rhAPC), 24 pg/kg/hour for 96 hours, was associated with a 6% absolute reduction in 28-day all-cause mortality compared with placebo according to a large placebo-controlled, randomized, clinical trial in patients with severe sepsis.[28] The treatment benefit was confined to patients with greatest disease severity, as indicated by a baseline APACHE II score higher than 25 or those with two or more organ failures at baseline.[48] [Jo] Retrospective analyses would suggest that patients with severe sepsis caused by community- acquired pneumonia and those with overt DIC may be the most ideal target populations for this agent.

The main adverse event associated with rhAPC is bleeding. Bleeding tends to occur in patients with severe thrombocytopenia and in those with a known disruption of blood vessels or ulcerative gastrointestinal lesions. RhAPC is not approved for children or surgical patients with sepsis and a single organ failure.[51] Children with purpura fulminans, a profound state of protein C deficiency caused by infection with Neisseria meningitidis or Streptococcus pneumoniae, should be considered for treatment with rhAPC given the high mortality rate and amputation rates associated with this syndrome.

Glycemic Control

Tight control of the blood glucose level during sepsis might be expected to decrease the rate of infectious complications and improve outcomes in patients with sepsis. Numerous clinical trials have shown that maintaining blood glucose level between 6.1 and 10mmol/l had better outcomes measured by improved survival, fewer blood stream infections, shorter ICU stays, and fewer episodes of acute renal failure." [56]

Ventilator Treatment for Acute Respiratory Distress

A randomized clinical trial has demonstrated lower mortality and an increase in the number of days off the ventilator when a lower (6 mL/kg) tidal volume strategy is used compared with a standard (12 mL/kg) tidal volume strategy." However a low PEEP and high PEEP strategies have been found to have similar outcomes.[58] A PEEP >5cmH20 is required to avoid lung collapse.[59] Nitric oxide and prone position ventilation have also been applied and found to have a transient improvements in oxygenation,[60 62] however their effects cannot be generalized. Many studies have recommended against the routine use of the pulmonary artery catheter for patients with ARDS due to lack of correlation of pulmonary artery occlusion pressures with clinical response.[63,64]

Blood Transfusions

Clinical data would suggest early use of transfusions in the acute setting of sepsis, followed by a conservative strategy once tissue oxygen demands have been reached. Haemoglobin of between 7 and 9 g/dl have been demonstrated to have equally good outcomes as traditional lOg/dl in maintenance of oxygen-carrying capacity.[65,66]

Additional Treatment Components

Three additional components in the care of severe sepsis patients include ensuring adequate nutrition, providing deep venous thrombosis prophylaxis, and providing gastric ulcer prophylaxis.[26] Adequate nutrition is best accomplished enterically to avoid catheter-related blood stream infections, maintain gut mucosa integrity, and prevent the theoretical possibility of translocation of bacteria across the intestinal wall. A mortality benefit with enteral feeds containing omega-3 fatty acids compared with standard enteral feeds was observed in a small clinical trial of patients with severe sepsis.[67] A morbidity benefit was observed with this same formula in patients with ARDS.[6ri] Deep venous thrombosis prevention can be accomplished with the use of subcutaneous heparin or continuous use of pneumatic compression stockings.[69, /0] Gastric ulcer prophylaxis may be accomplished with sucralfate, an H2 receptor antagonist, or a proton pump inhibitor.[26] The benefit of prevention of upper gastrointestinal bleeding should be weighed against the

potential effect of increased gastric pH on greater incidence of ventilator-associated pneumonia/[1]

Prevention of severe sepsis and septic shock

Because pneumonia is the most common infection leading to sepsis, efforts to decrease the incidence of this infection would lead to the most rapid reduction in new sepsis cases. Every effort should be made to vaccinate susceptible individuals against influenza, H. influenzae, and S. pneumoniae. Additionally, asplenic patients should receive vaccination against N. meningitidis as should college students living in dormitories. The incidence of intravascular catheter-related blood stream infections can be diminished by strict procedures to ensure sterile insertion, as well as the use of chlorhexidine dressings at the exit site. Cases of ventilator-associated pneumonia can be decreased by maintaining ventilator patients semirecumbent at a 45-degree angle. This also limits aspiration risk/[2] Administration of enteral vancomycin has also been shown to prevent ventilator-associated pneumonia/[3, n]

SURVIVING SEPSIS CAMPAIGN (SSC)

Surviving Sepsis campaign, which is targeted to reduce mortality from sepsis over the coming years, was adopted at the Society of Critical Care Medicine's 33rd Annual Conference in Orlando, Florida.

The SSC aimed to reduce mortality from sepsis via a multi-point strategy, including building awareness of sepsis, improving diagnosis, increasing the use of appropriate treatment, educating healthcare professionals, improving post-ICU care, developing guidelines of care, and facilitating data collection for the purposes of audit and feedback.

Choosing therapies to treat patients with severe sepsis and septic shock requires an organized approach to evaluating the evidence. The Sepsis Resuscitation and Management Bundles were derived from the 2008 Surviving Sepsis Campaign Guidelines which incorporated the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system approach to evaluating the literature.

Understanding the Bundle Concept

A "bundle" is a group of therapies for a given disease that, when implemented together, may result in better outcomes than if implemented individually. In a bundle, the individual elements included are built around best evidence-based practices. The science supporting the individual treatment strategies in a bundle is sufficiently mature such that implementation of the approach should be considered either best practice or a reasonable and generally accepted practice.

The purpose of creating a bundle strategy is to clearly articulate a therapeutic framework that will function as a lever for change.

The Severe Sepsis Bundles have been designed with the hope to allow teams

to follow the timing, sequence, and goals in the bundles, to achieve a 25 percent reduction in mortality due to severe sepsis or septic shock.

There are two Severe Sepsis Bundles. Each bundle articulates objectives to be accomplished within specific timeframes. The bundles have been developed based upon the 2008 Surviving Sepsis Campaign Guidelines for the Management of Severe Sepsis and Septic Shock. The Guidelines incorporated an evidence-based review of the literature and ranked the strength of each recommendation.

Sepsis Resuscitation Bundle

The Sepsis Resuscitation Bundle describes seven tasks that should begin immediately, but must be accomplished within the first 6 hours of presentation for patients with severe sepsis or septic shock. Some items may not be completed if the clinical conditions described in the bundle do not prevail in a particular case, but clinicians should assess for them. The goal is to perform all indicated tasks 100 percent of the time within the first 6 hours of identification of severe sepsis.

Bundle Element 1

Measure serum lactate

Bundle Element 2

Obtain blood cultures prior to antibiotic administration

Bundle Element 3

Administer broad-spectrum antibiotic within 3 hours of ED admission and within 1 hour of non-ED admission

Bundle Element 4

Treat hypotension and/or elevated lactate with fluids

In the event of hypotension and/or serum lactate >4 mmol/L:

- Deliver an initial minimum of 20 mL/kg of crystalloid or an equivalent
- Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) >65 mm Hg

Apply vasopressors for ongoing hypotension

Bundle Element 5

Maintain adequate central venous pressure
Maintain adequate central venous oxygen saturation

In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate >4 mmol/L:

- Achieve a central venous pressure (CVP) of >8 mm Hg
- Achieve a central venous oxygen saturation (Scv02) >70% or mixed venous oxygen saturation (Sv02) >65%

Sepsis Management Bundle

Evidence-based goals that must be completed within 24 hours for patients with severe sepsis, septic shock and/or lactate > 4 mmol/L (36 mg/dL). For patients with severe sepsis, as many as four bundle elements must be accomplished within the first 24 hours of presentation. Some items may not be completed if the clinical conditions described in the bundle do not prevail, but clinicians must assess for them. The goal is to perform all indicated tasks 100 percent of the time within the first 24 hours of presentation:

Bundle Element 1

Administer low-dose steroids for septic shock in accordance with a standardized ICU policy.
If not administered, document why the patient did not qualify for low-dose steroids.

Bundle Element 2

Administer recombinant human activated protein C (rhAPC) in accordance with a standardized ICU policy. If not administered, document why the patient did not qualify for rhAPC.

Bundle Element 3

Maintain glucose control lower limit of normal, but <180 mg/dL(10 mmol/L)

Bundle Element 4

Maintain a median inspiratory plateau pressure (IPP) <30 cm H20 for mechanically ventilated patients

2.0 OBJECTIVE OF STUDY

General Objective

To determine the clinical practice patterns on the management of severe sepsis and septic shock by anaesthesia practitioners at Kenyatta National Hospital (KNH)

Specific objectives

1. To determine fluid administration practices in severe sepsis and septic shock
2. To establish the practices in the antimicrobial therapy use
3. To determine the practice as regards the red blood cell transfusion triggers
4. To determine the practices in the use of inotropes
5. To determine the monitoring aspects practice and resuscitation end-points
6. To find out the limitations in the management of severe sepsis and septic shock

3.0 JUSTIFICATION OF THE STUDY

In 2009, 999 patients were admitted to Kenyatta National hospital, critical care unit. Severe sepsis and septic shock contributed 8% of admissions with a mortality rate of up to 70%.[1]

The management of sepsis in hospitals is significantly better today than it was 30 years ago. However, sepsis-associated mortality rates still remain high.

The recent improvements in outcomes has been characterised by the successive introduction of multiple interventions and therapies which has been as a result of a better understanding of the pathophysiology of sepsis.

The annualized incidence of sepsis is increasing by 8%. The incidence of severe sepsis is increasingly greatest in older adults. The increase is believed to be caused by the increased use of invasive procedures, immunosuppressive drugs , chemotherapy, transplantation, and prosthetic implants and devices and also due to the increasing problem of antimicrobial resistance.

The Surviving Sepsis Campaign (SSC) was developed to improve the management, diagnosis and treatment of sepsis. The SSC aimed to reduce mortality from sepsis via a multi-point strategy including developing guidelines of care. In addition, many reviews have been done elsewhere looking at different aspects of management of sepsis. No study has been undertaken locally to determine the current practises in the management of sepsis and the adherence to SSC guidelines.

Further, the study aims to identify the common problems and limitations to management of sepsis in KNH and thus form a basis for the establishment of protocols for its management.

4.0 STUDY METHODOLOGY

Type of study

The study was designed as a cross sectional descriptive survey by a self-completion questionnaire accompanied by an explanation letter and consent form.

Study population

Anaesthesia practitioners at Kenyatta National Hospital, critical care unit, were the study population. These included physician anaesthesiologists and part two postgraduate students undertaking Master of Medicine anaesthesia program.

Sample size

Simple systematic sampling was applied to include as many of the consultant anaesthesiologists, as well as the senior post-graduate residents undertaking their Masters Degree program in anaesthesia.

Since the study population in this study was less than 10000, the sample size was calculated as follows:[/b]

$$n = \frac{Nz^2pq}{[d^2(N-I)+z^2pq]}$$

where

n is the desired sample size

z is the standard normal deviation at the required confidence level, in this case 1.96

p is the proportion in the target population estimated to have characteristics being measured. Since there is no estimate available of the proportion in the target population assumed to have the characteristics of interest, 50% (0.5) was used as recommended by Fisher et al.[/s]

q is l-p= 0.5

d is the level of statistical significance set =0.05

N is the estimate of the population size, which in this case is the number of anaesthesia practitioners in KNH. They include 35 consultant anaesthesiologists and 20 part two post graduate students in the Master of medicine anaesthesia program. The total is 55.

Therefore;

$$n = \frac{55 \times (1.9S)^2 \times (0.5) \times (0.5)}{[(0.05)^2 (51-1) + (1.96^2 \boldsymbol{X} 0.5 * 0.5)]}$$

$$= 50.72$$

Therefore the desired sample size for this study was 51

Inclusion criteria

Anaesthesia practitioners working in KNH from whom consent to be included in the study was obtained.

Exclusion criteria

Anaesthesia practitioners from whom consent to be included in the study was not obtained.

Post-graduate students in part one of Master of Medicine anaesthesia program

Study site

The study was carried out at Kenyatta National Hospital anaesthesia department. KNH is a teaching and referral hospital located in Nairobi, the capital city of Kenya. It has a 21 bed capacity CCU.

Data collection tool

Self-administered questionnaire which was hand delivered and collected on the same day of issuance to the participants of the study.

Study method

After getting approval from Kenyatta National Hospital/University of Nairobi, Ethics and Research Committee, a questionnaire was administered to anaesthesia practitioners working in the critical care unit, who gave consent to be included in this study. The survey sought to determine the current practice in the management of severe sepsis and septic shock by the practitioners. The limitations and challenges faced in the management of severe sepsis and septic shock were also surveyed. The participant received a questionnaire, which they filled and returned within a day. The data was then recorded electronically, analyzed and presented in both graphical and text formats.

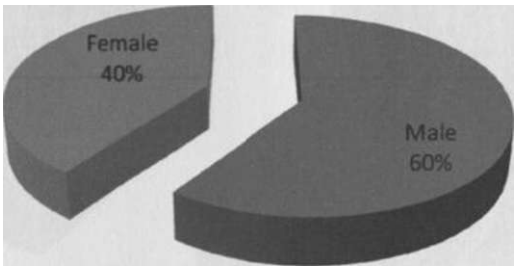
Ethical considerations

1. The nature and purpose of the study was explained to the participants in the study and consent obtained.
2. The study had no harmful effects on the participants, patients or the hospital in general.
3. Confidentiality was maintained.
4. Permission was sought from Kenyatta National Hospital-University of Nairobi, Ethics and Research Committee before undertaking the study.
5. There were no cost implications to the participants at any point during the study.
6. Findings from the study will be availed to the Ethics Committee of KNH and the University of Nairobi.

5.0RESULTS

Respondents in the survey comprised both the consultant anaesthesiologist and part two anaesthesia residents. Figure 1 illustrates the gender distribution of respondents. Male participants were twenty seven (27) representing 60% of respondents; female participants were eighteen (18) representing 40% of respondents. This represents a male to female ratio of 3:2.

Fig 1: Gender Distribution of respondents



The age distribution of participants was as follows; twenty (20) participants were between 25-34 years (44.4%), fourteen (14) were between 35-44 years (31.1%), nine (9) between 45-54 years (20%) and two (2) aged 54 years and above (4.4%). This is illustrated in figure 2.

Fig 2: Age distribution of participants

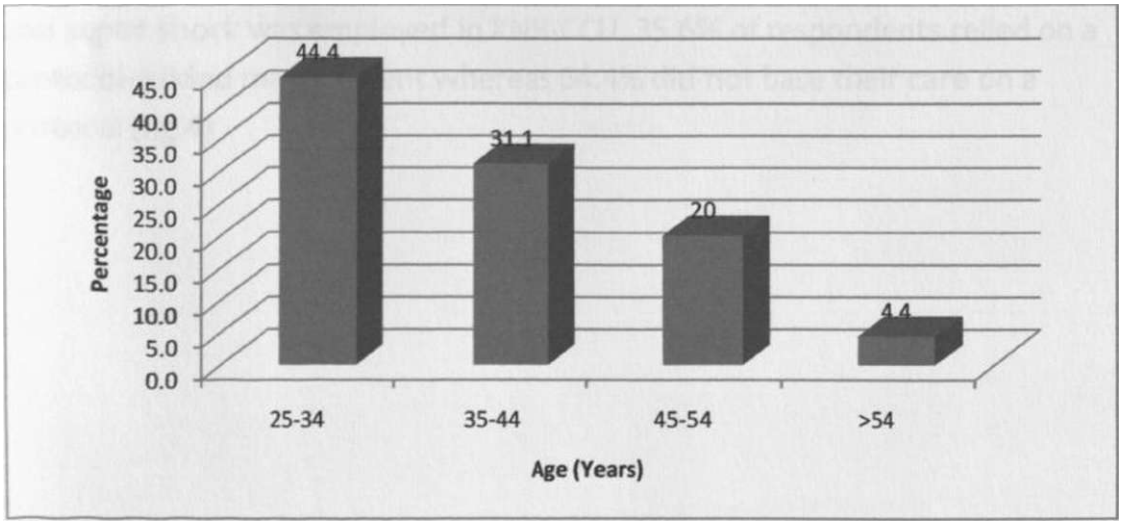
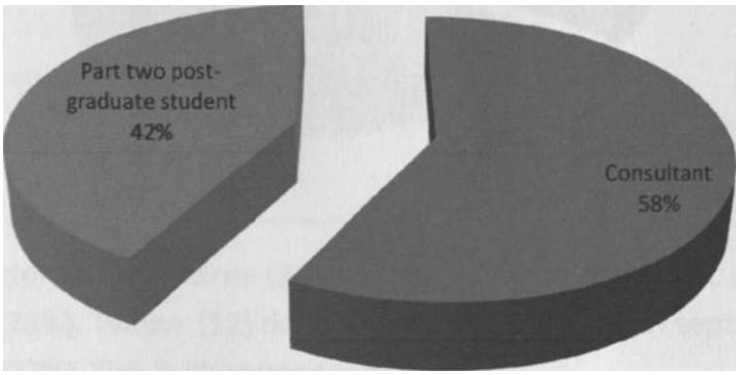


Figure 3 illustrates the percentage cadre of anaesthesia practitioners surveyed The consultant anaesthesiologists were twenty six (26) representing 57.8% of respondents and part two post-graduate anaesthesia residents were nineteen (19) representing 42.2% of respondents. Total number of practitioners sampled was 45, representing an 88% response rate of the calculated sample.

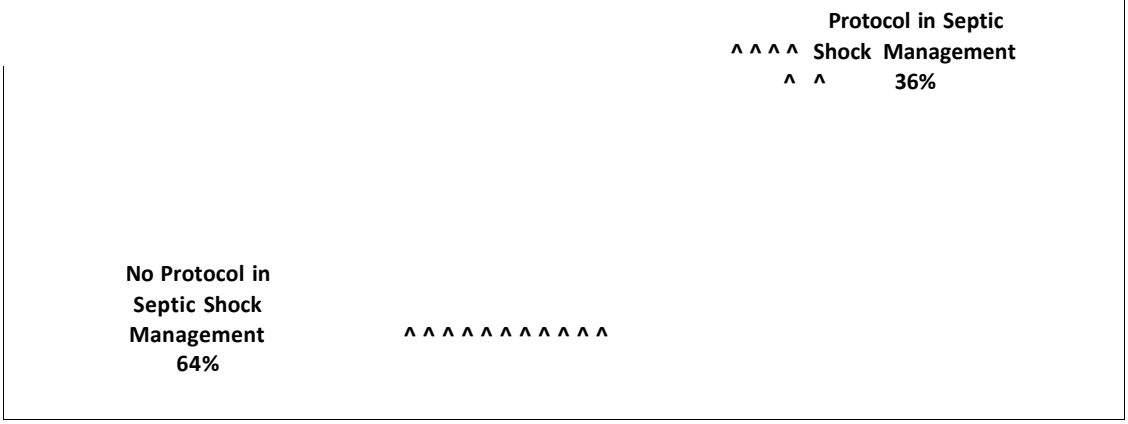
Fig 3: Percentage Cadre of study participants



The mean number of years of anaesthesia practice among consultant anaesthesiologist participants was ten (10) years.

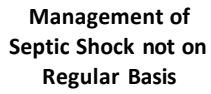
Data was collected on whether protocol-guided management of severe sepsis and septic shock was employed in KNH-CCU. 35.6% of respondents relied on a protocol-guided management whereas 64.4% did not base their care on a protocol (fig 4)

Fig 4:lltilization of Protocol in Septic Shock Management



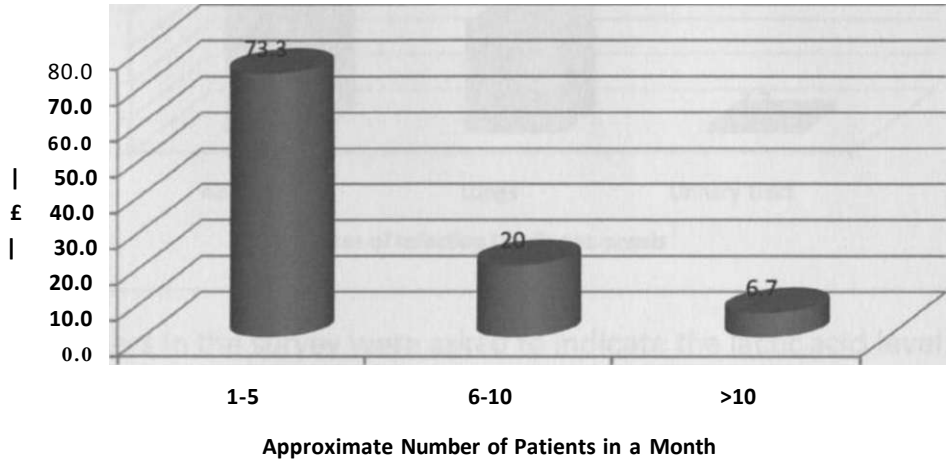
Of the respondents, thirty three (33) manage patients with septic shock on a regular basis (73%). Twelve (12) do not manage patients with septic shock on a regular basis (27%). This is illustrated in figure 5.

Fig 5: Regularity of respondents in Septic Shock Management



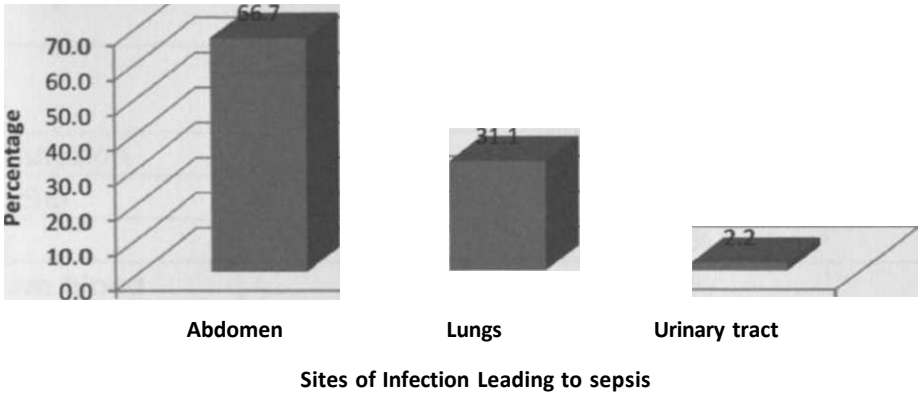
Data was collected on the approximate number of patients with severe sepsis and septic shock managed by the respondents in a month. Thirty three (33) participants managed between 1-5 patients representing 73.3% of respondents, nine (9) managed between 6-10 patients representing 20% and three (3) managed more than 10 patients (6.7%). This is shown in figure 6.

Fig 6: Number of patients with severe sepsis and septic shock managed by the respondents in a month



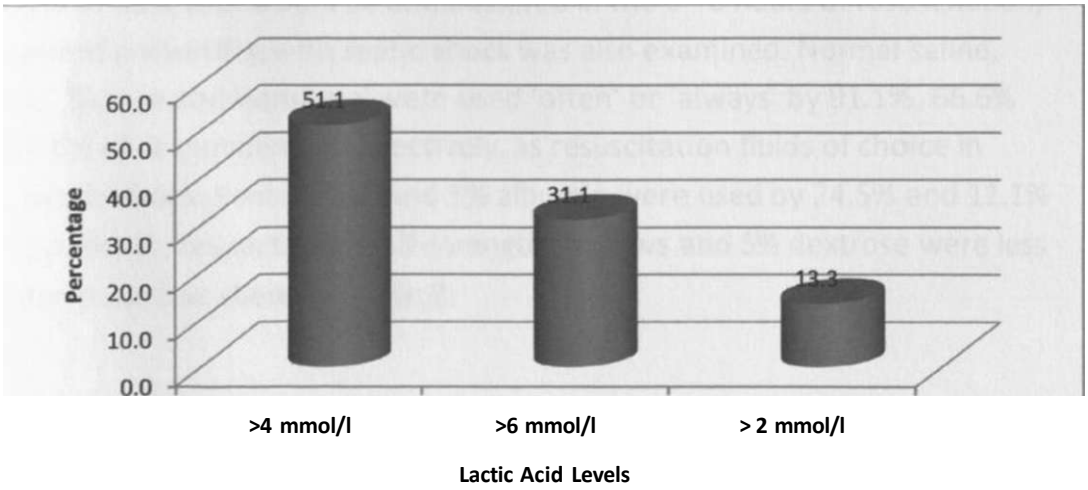
The most common site of infection leading to sepsis was examined and responses illustrated in figure 7. Only 31.1% respondents stated it was the lungs. 66.7% felt it was the abdomen and 2.2% the urinary tract.

Fig 7: Most common site of infection leading to sepsis



The practitioners in the survey were asked to indicate the lactic acid level, above which would indicate tissue hypoxia in patients with sepsis. About half of respondents, 51.1% stated a lactic acid level > 4mmol/l. This is shown in figure 8.

Fig 8: Lactic acid level above which would indicate tissue hypoxia



The following monitoring parameters were found to be necessary or mandatory in sepsis by most of the respondents with an exception of telemetry and pulmonary artery catheter. However, none of the parameters had a 100% response rate among all practitioners sampled. This is shown in table 1.

Table 1: Importance of monitoring parameters in sepsis

	Number of respondents	Percentage of respondents
Oxygen saturation	40	88.9%
Foley catheter	41	91.1%
Telemetry	16	35.6%
Non-invasive blood pressure	41	91.1%
Intra-arterial blood pressure	38	84.5%
Central venous pressure	42	93.3%
CVP with continuous $Scv0_2$	31	68.9%
Pulmonary artery catheter	13	28.0%

The type of fluid that would be administered in the 1st 6 hours of resuscitation, in a patient presenting with septic shock was also examined. Normal saline, Ringers' lactate and Hemacael were used 'often' or 'always' by 91.1%, 66.6% and 61.0% of respondents, respectively, as resuscitation fluids of choice in early septic shock. Pentastarch and 5% albumin were used by 24.5% and 11.1% of respondents, respectively. Half-strength Darrows and 5% dextrose were less commonly used as shown in table 2.

Table 2: Fluid administration practices in early septic shock

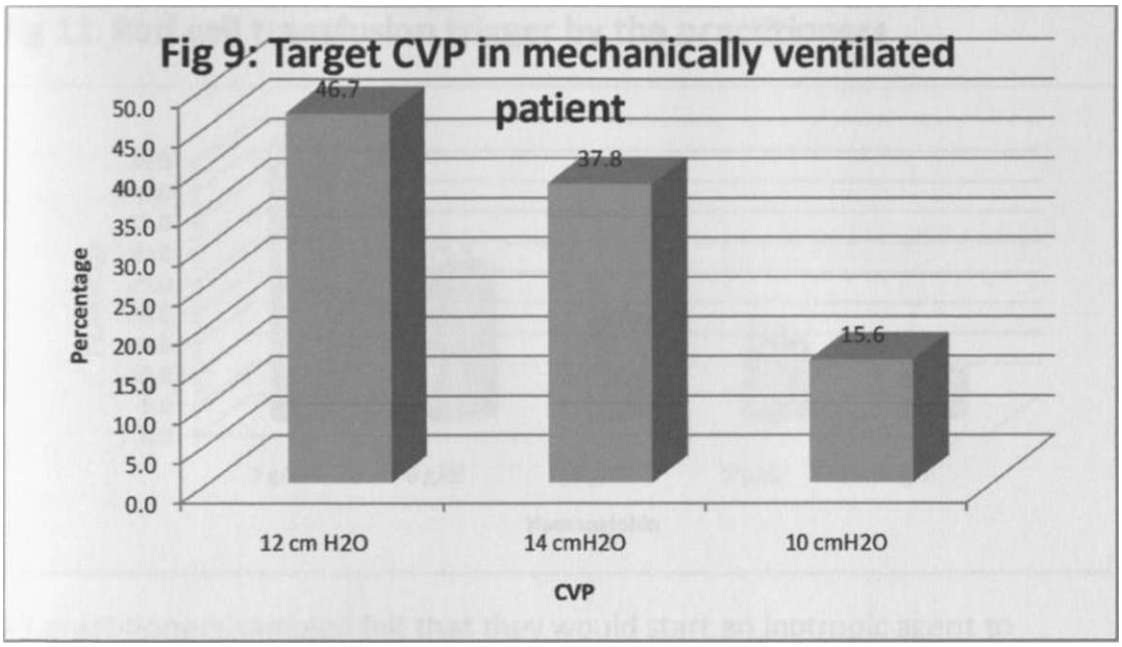
	Number of respondents	Percentage of respondents
Normal saline	41	91.1%
Ringers' lactate	30	66.6%
Half-strength Darrows	2	4.4%
5% dextrose	2	4.4%
5% albumin	5	11.1%
Pentastarch	11	24.5%
Hemacael	27	61.0%

Study participants reported use of several resuscitation end-points 'often' or 'always' to evaluate whether a patient was adequately volume resuscitated in the early phases of septic shock. Urine output, peripheral perfusion and CVP were used most frequently by respondents each 93.3%, followed by blood pressure by 91.1% of respondents. Heart rate was used by 84.4% of respondents. Cardiac output/index and $Scv0_2$ were less commonly used as shown in table 3.

Table 3: End-points for evaluation of adequacy of volume resuscitation in early septic shock

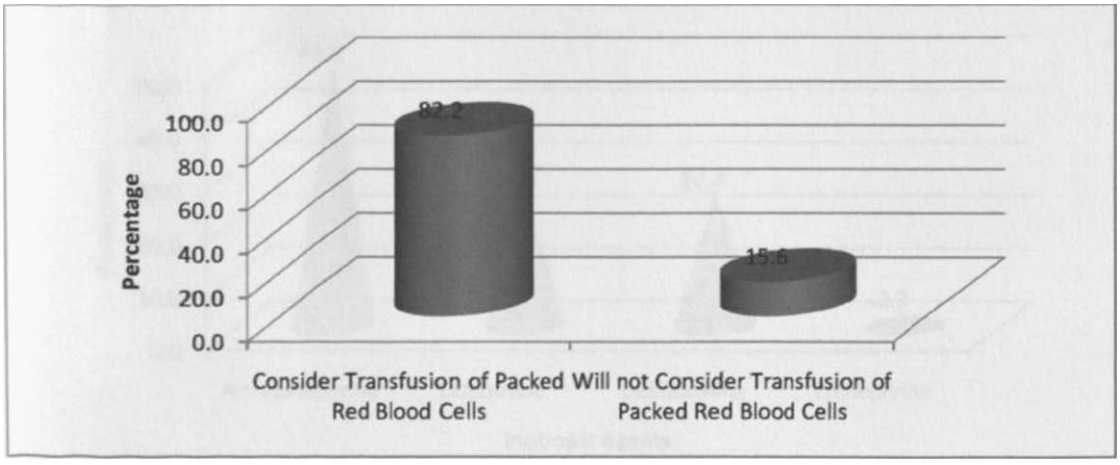
	Number of respondents	Percentage of respondents
Heart rate	38	84.4%
Blood pressure	41	91.1%
Peripheral perfusion	42	93.3%
Urine output	42	93.3%
CVP	42	93.3%
$Scv0_2$	23	51.1%
Cardiac output/ index	24	53.3%

During initial fluid resuscitation, the target CVP in a mechanically ventilated patient was sought. Most of the practitioners sampled, 46.7% stated the target CVP to be 12cmH_20 as illustrated in figure 9.



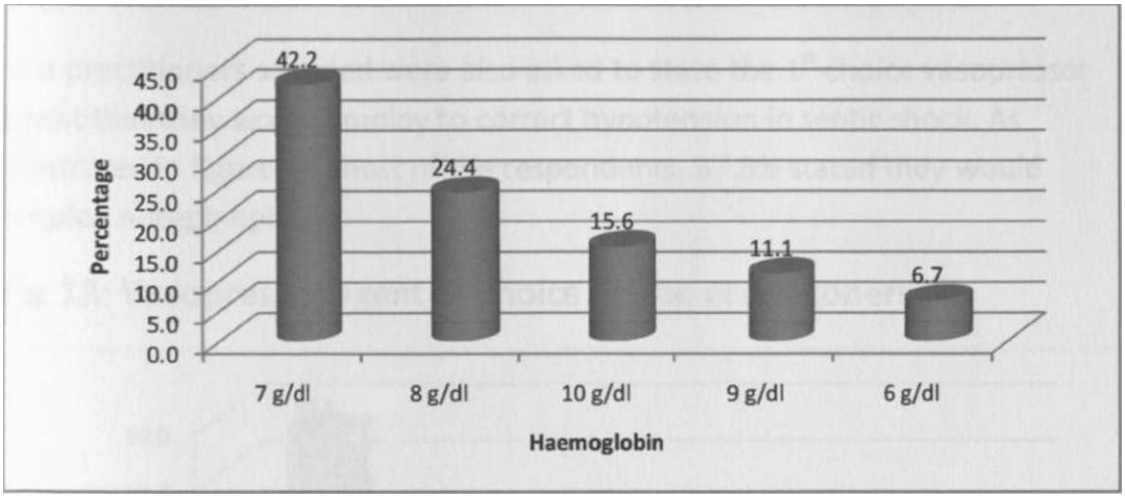
The practitioners sampled were asked if the central venous saturation ($Scv0_2$) of 70% was not achieved after fluid resuscitation to target CVP, whether they would consider transfusion of packed red cells, with 82.2% stating they would. This is as shown in figure 10.

Fig 10: Transfusion of packed red cells to achieve $Scv0_2$ of 70%



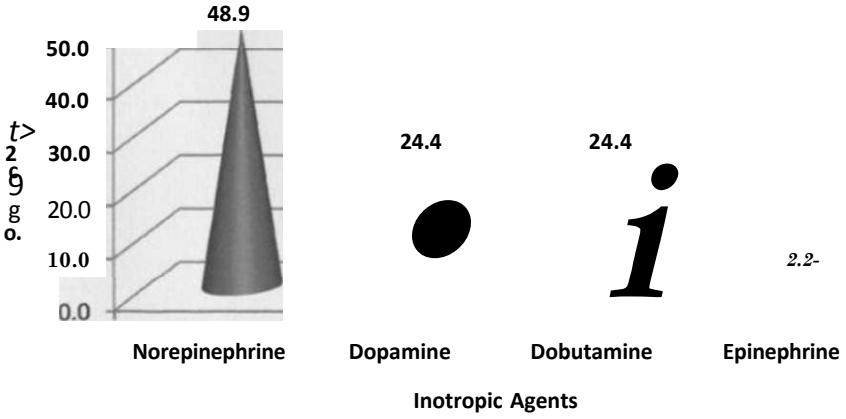
Information regarding the lowest haemoglobin trigger that practitioners sampled would use to administer a red blood cell transfusion was sought. Most of the practitioners, 42.2% used a trigger of 7g/dl as illustrated in figure 11.

Fig 11: Red cell transfusion trigger by the practitioners



All practitioners sampled felt that they would start an inotropic agent to further increase oxygen delivery, if the central venous saturation (Scv02) was still below the set goal of >70% in an adequately volume resuscitated patient and after a red cell transfusion. Of the respondents, 48.9% would recommend nor epinephrine to achieve this. Dopamine and dobutamine was each recommended by 24.4% of the practitioners sampled. Epinephrine was only recommended by 2.2% as illustrated in figure 12.

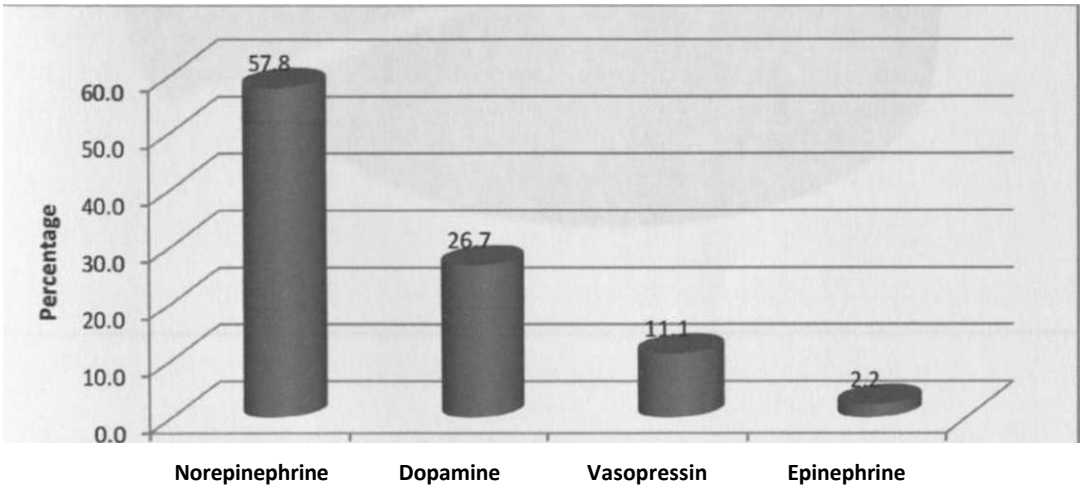
Fig 12: Inotropic agent of choice by the practitioners



All practitioners sampled felt that empirical intravenous combination antibiotic therapy should be started within the 1st hour of recognition of severe sepsis and septic shock. De-escalation to the most appropriate single therapy after susceptibility profile is known was also recommended by all the respondents.

The practitioners sampled were also asked to state the 1st choice vasopressor agent that they would employ to correct hypotension in septic shock. As illustrated in figure 13, most of the respondents, 57.8% stated they would employ norepinephrine.

Fig 13: Vasopressor agent of choice by the practitioners



Information regarding whether the practitioners sampled would recommend a conservative fluid strategy for patients with established ALI/ARDS was sought. 64% of the respondents felt they would recommend a conservative fluid strategy for these patients as shown in figure 14.

Fig 14: Conservative fluid strategy for established ALI/ARDS

Various challenges were faced by the practitioners surveyed, and the responses are illustrated in table 4. Different challenges held different weight to the respondents. 82.0% of the respondents felt limited CCU bed space for admission to be a major challenge while at the end of the spectrum, 31.1% of the respondents felt non-applicability of results in management to be a major challenge.

Table 4: Challenges in severe sepsis and septic shock management

	Number of respondents	Percentage of respondents
Limited CCU bed space	37	82.0%
Delay in surgical intervention when needed	33	73.3%
Unavailability of diagnostic tests	28	62.2%
; Inadequate multi-disciplinary support	26	57.8%
Delay in making definitive diagnosis	25	55.6%
Delay in getting the lab results to aid management	24	53.3%
Lack of pharmacological agents needed in management	19	42.2%
Lack of monitoring equipments/parameters	16	35.6%
Non-applicability of results in management	14	31.1%

6.0 DISCUSSION

Management of severe sepsis and septic shock has been the subject of immense debate especially in the last 10 years. This is owing to a better understanding of the pathophysiology of sepsis which has led to successive introduction of multiple interventions and therapies. This has in effect led to better outcomes.

The main aim of the survey was to determine the clinical practice patterns in the management of severe sepsis and septic shock at the Kenyatta National Hospital and the adherence to the surviving sepsis campaign guidelines with a view of identifying challenges in the management. Kenyatta National Hospital was chosen as the study site because it is the premier training and referral institution with the largest critical care unit in the country.

Septic shock management is usually carried out in a critical care setting. In Kenya, CCU remains under the guidance of anaesthesiologists mainly and for this reason they comprised the study population.

Male participants were 60% with female participants making up 40%. This represents a male to female ratio of 3:2. Litswa LA in a 2003 country wide survey of physician anaesthesiologists found the male to female ratio to be ~ 3:2.[J] This reveals minimal gender disparity in the anaesthesia fraternity.

The cadre of study participants was fairly distributed with consultant anaesthesiologists making up 58% and part two postgraduate anaesthesia students making up 42%.

The survey was characterized by an 88% response rate. This indicates a fairly representative sample of the anaesthesia practitioners in Kenyatta National Hospital.

Of the respondents, 27% did not manage patients with severe sepsis and septic shock on a regular basis. Also, 73.3% of the respondents managed between 1-5 patients with sepsis in a month. Most of these respondents were consultant anaesthesiologists who their main area of duty is the operating theatres or are involved in administrative responsibilities. This may not place consultants in close contact with these patients on a daily basis. Despite the bias created by

this, data so obtained was still analyzed with the premise that the responses were in reference to the care that would be given by the respondents, whether they be in active CCU duty or not. However, the care given to septic patients while undergoing surgical interventions in operating theatres is still part of a continuum of their long term care in the CCU.

Sixty seven percent (67%) of the respondents felt the abdomen to be the most common site of infection leading to sepsis. This is in contrast to a study conducted by Bernard GR et al which revealed the lungs to be the most common site of infection leading to sepsis, followed by the abdomen and the urinary tract.[28]

Nearly half of the respondents (44.6%) incorrectly stated the lactic acid levels, above which would indicate tissue hypoxia in patients with sepsis. This could be attributed to the unavailability of this laboratory test in Kenyatta National Hospital. The surviving sepsis campaign guidelines recommend aggressive resuscitation in patients with blood lactate concentration >4 mmol/l.[77]

The results of the survey cited central venous pressure (CVP), non invasive blood pressure (NIBP), Foley catheter and oxygen saturation as the most important monitoring parameters in sepsis by the respondents. CVP with continuous $Scv0_2$was cited by 68.9% of the respondents. Interestingly, only 35.6% felt the need for telemetry with pulmonary artery catheter cited by 28.0%. This compares favourably with a similar study conducted by Canadian critical care trials group at tertiary care university affiliated and community Canadian hospitals with the only difference been a preference of intra-arterial blood pressure monitoring in this study as opposed to non-invasive blood pressure/[8] According to the surviving sepsis campaign guidelines all patients requiring vasopressors should have an arterial catheter placed if resources are available. This is because an arterial cannula provides a more appropriate and reproducible measurement of arterial pressure.

Use of either intermittent or continuous measurements of Scv02 was judged to be acceptable.[77] Two multicenter randomized trials failed to show benefit with the routine use of pulmonary artery catheter in patients with sepsis.[6"] This was due to lack of correlation of pulmonary artery occlusion pressures

with clinical response and absence of a proven strategy to use catheter results to improve patient outcomes.

Normal saline and Ringers' lactate and colloidal fluid hemacael were preferred by the respondents in the 1st 6 hours of resuscitation of patients with severe sepsis and septic shock. 5% albumin and pentastarch were used less frequently, and their erratic availability could be a contributing factor. The Saline versus 4% Albumin Fluid Evaluation (SAFE) study indicated that albumin administration was safe and equally as effective as crystalloid.[35] Indeed, there was an insignificant decrease in mortality rates with the use of colloid in a subset analysis of septic patients. Use of pentastarch has been associated with increased risk of acute renal failure in patients with sepsis, though variable findings preclude definitive recommendations. " As the volume of distribution is much larger for crystalloids than for colloids, resuscitation with crystalloids requires more fluid to achieve the same end points.

Urine output, CVP, peripheral perfusion and blood pressure were cited as the most common volume resuscitation end points. Only 51.1% reported they would use central venous saturation (Scv02) as a volume resuscitation end point. The low adoption of Scv02 may relate to lack of resources. This compares with a survey of 30 academic emergency room physicians from the USA, where only 7% reported use of early goal-directed therapy in the emergency room with the major barrier being lack of specialty monitoring equipment.[79] According to the surviving sepsis guidelines, the goals of initial resuscitation should include a central venous pressure of 10-16 cmH_20, mean arterial pressure > 65 mmHg, urine output > 0.5ml/kg/hr and central venous saturation >70% as one part of a treatment protocol/'

Only 37.8% of the respondents felt that the target CVP in a mechanically ventilated patient during initial fluid resuscitation should be > 14cmH20. In surviving sepsis campaign guidelines, a higher target CVP of > 14cmH20 is recommended to account for the impediment to filling, in mechanically ventilated patients or in patients with known pre-existing decreased ventricular compliance.[7/]

Eighty two percent (82%) of the respondents said they would consider transfusion of packed red blood cells, if a central venous saturation (Scv02) of

70% is not achieved after fluid resuscitation to target CVP. All the respondents would start an inotropic agent if the Scv02 was still below 70% after above measures. In the early goal-directed therapy trial, if Scvo2 of 70% was not achieved with fluid resuscitation to target CVP, then transfusion of packed red cells to achieve a hematocrit of >30% or administration of an inotropic agent was used to achieve this goal.[34] This protocol was associated with an improvement in survival. However, it was not clear on the relative contribution of these two components of the protocol on achievement of improved outcome.

Only 24.4% of the respondents recommended the use of dobutamine as the inotropic agent of choice to achieve the above mentioned goals. According to the surviving sepsis campaign guidelines, dobutamine is the first-choice inotrope for patients with measured or suspected low cardiac output in the presence of adequate left ventricular filling pressure or clinical assessment of adequate fluid resuscitation.[7']

Forty two percent (42%) of the respondents said they would use a haemoglobin transfusion trigger of 7g/dl with 24.4% saying they would use a trigger of 8g/dl. This compares with a study conducted in Canadian hospitals where 76.8% would use a haemoglobin transfusion trigger of 8g/dl or less/[8] The acceptance of a lower transfusion trigger could probably relate to the findings of the Transfusion Requirements in Critical Care trial which suggested that haemoglobin of 7-9 g/dl when compared with 10-12 g/dl was not associated with increased mortality in adults/''

The survey revealed that all the respondents indicated that empirical intravenous combination antibiotic therapy should be started as soon as possible and within the l[i l] hour of recognition of septic shock or severe sepsis and that de-escalation to the most appropriate single therapy after susceptibility profile is known is to be recommended. This is satisfactory because these are the guidelines as per the surviving sepsis campaign.[77]

Majority of the respondents, 57.8% would employ norepinephrine as the 1st choice vasopressor agent to correct hypotension in septic shock, with 26.7% using dopamine. This is as per the surviving sepsis campaign guidelines which recommend either norepinephrine or dopamine as the 1st choice vasopressor

agent to correct hypotension in septic shock/ ' However, norepinephrine is more potent than dopamine and is more effective at reversing hypotension in these patients.

Sixty four percent (64%) of the respondents said they would recommend a conservative fluid strategy for patients with established ALI/ARDS. Small prospective studies in patients with ALI have suggested that strategies directed at minimizing fluid infusion and weight gain are associated with improved oxygenation, fewer days of mechanical ventilation and decreased CCU length of stay.[38]

Respondents indicated several challenges and limitations faced in the management of patients with severe sepsis and septic shock at KNH. Limited CCU bed space was the limitation cited most by the respondents. Other challenges faced most include delay in surgical intervention when needed, unavailability of diagnostic tests, inadequate multi-disciplinary support and lack of monitoring equipments. In a survey of 30 academic emergency room physicians from USA, major reported barriers in management of septic shock included the need for specialty monitoring equipment, amount of resources needed, the need for central venous catheter cannulation and too much emergency physician time required.[79]

7.0 CONCLUSION

The most common fluids administered in the l'[1] 6 hours of resuscitation by the respondents were Normal saline, Ringers' lactate and Hemacael.

All practitioners start empirical intravenous combination antibiotic therapy within the l[i l] 1 hour of recognition of severe sepsis and septic shock with de-escalation to the most appropriate single therapy after susceptibility profile is known.

82.2% of the practitioners would start transfusion of packed red cells if the central venous saturation ($Scv0_2$) of 70% was not achieved after fluid resuscitation to target CVP.

About half of the practitioners use a haemoglobin trigger of 7g/dl to administer a red blood cell transfusion.

All the practitioners would start an inotropic agent to further increase oxygen delivery, if the $Scv0_2$ was still below the set goal of >70% in an adequately volume resuscitated patient and after a red cell transfusion. Only 24.4% of the practitioners would use dobutamine to achieve this.

Norepinephrine was the vasopressor agent of choice by most practitioners.

Central venous pressure(CVP), non-invasive blood pressure(NIBP), foley catheter and oxygen saturation are the monitoring parameters cited as most important in sepsis.

Urine output, peripheral perfusion, CVP and blood pressure are the resuscitation end-points often used to evaluate whether a patient was adequately volume resuscitated in the early phases of septic shock.

Limited CCU bed space, delay in surgical intervention when needed and unavailability of diagnostic tests were the challenges faced most by the practitioners in the management of severe sepsis and septic shock.

8.0 RECOMMENDATIONS

1. KNH should come up with a protocol to guide management of severe sepsis and septic shock.
2. Continuous medical education to all members of the care team on the current recommended practices is required.
3. Challenges faced in the care of patients with severe sepsis and septic shock should be addressed with a view of optimizing resources available.
4. Further studies should be conducted on this area, especially on the effect of current recommended practices on patient outcome.

9.0 STUDY LIMITATIONS

Not all anaesthesia practitioners were included in the survey hence the views of those not included was missed. However, effort was made to get as representative a sample as possible.

Several omissions were present in some sections of the questionnaire due to inability to provide answers by some respondents. Analysis of the data was made on those valid entries alone. Confidentiality was maintained during the course of the study.

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APPENDIX 3

INFORMED CONSENT FORM

A SURVEY OF THE PRACTICE IN THE MANAGEMENT OF SEVERE SEPSIS AND SEPTIC SHOCK BY ANAESTHESIA PRACTITIONERS AT THE KENYATTA NATIONAL HOSPITAL CRITICAL CARE UNIT

This Informed Consent Form is for practitioners who work in the critical care unit at the Kenyatta National Hospital. You are hereby invited to participate in the above mentioned study

PART I: *Information Sheet*

Introduction

I am Dr. David Chomba Mwai, a third year resident in the MMed Anaesthesia program. I am conducting a review on the management of severe sepsis and septic shock at the Kenyatta National Hospital Critical Care Unit in part fulfillment of my post-graduate program requirements. I will strive to answer any queries that may arise before and during the course of the intended study.

Purpose of the research

The objective of this survey is to assess the practice of severe sepsis and septic shock management amongst anaesthesia practitioners at the Kenyatta National Hospital, Critical Care Unit. Specifically the study is to find out the fluid administration practices, antimicrobial therapy use, red cell transfusion triggers, use of inotropes, role of steroids, monitoring aspects and resuscitation end-points. It will further aid in highlighting the challenges faced in trying to improve the care offered to such patients who represent a significant proportion of admissions to the critical care unit.

Research Intervention

This research will not involve any interventions

Participant selection

You were selected to join the study using the stratified random selection.

Voluntary Participation

Your participation in this research is entirely voluntary. You are free to withdraw from the study.

Duration

The research is intended to take place between March and June 2011. During that time questionnaires will be distributed to all selected participants and submitted back on the same day.

Risks

By participating in this research you will not be exposed to any risk.

Benefits

The benefits from the study are mainly towards improving the care offered to severe sepsis and septic shock patients in the best manner, using the resources at hand.

Confidentiality

The information that I collect from this research project will be kept confidential. Any information about you will have your initials to which a serial number will be assigned instead of your name.

Who to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, please use the contacts below:

Dr.David Chomba Mwai (Researcher) - 0720 267048

Dr.Julius M Muriithi (Supervisor) - 0722 850375

This proposal has been reviewed and approved by the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee.

PART II: *Certificate of Consent*

I have read the foregoing information. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I hereby consent to participate in this research.

Name of Participant:

Signature:.....Date:

Statement by the researcher

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Name of Researcher:

Signature:.....Date:

APPENDIX 3

QUESTIONNAIRE

Below are questions and statements with reference to your practice of management of severe sepsis and septic shock in ICU. Mark the appropriate check boxes provided and make entries where applicable.

Serial Number:. . . . . .Date:

l.SEX: Male ( ) Female ( )

2. AGE: a) 25-34 yrs ( ) b) 35-44 yrs ( )

c) 45-54 yrs ( ) d) >54 yrs ( )

3. What cadre of anaesthesia practitioner?

a) Consultant anaesthesiologist ( ) Years of anaesthesia practice

b) Part two post-graduate anaesthesia student ( )

4. Have undergone any sub-speciality training?

a) Yes ( ) b) No ( )

If yes, what sub-speciality?

5. Is management of patient with severe sepsis and septic shock in KNH CCU guided by a protocol? Yes ( ) No ( )
6. Do you get to manage these patients on a regular basis?
a)Yes ( ) b) No ( )
7. What is the approximate number of such patients that you see in a month?

None ( ) 1-5 ( ) 6-10 ( ) >10 ( )

8. In your opinion, which is the most common site of infection leading to sepsis?
Lungs ( ) Abdomen ( ) Urinary tract ( ) Others

9. Which lactic acid levels, above which would indicate tissue hypoxia in patients with sepsis?

   >lmmol/l ( ) >4mmol/l ( ) >6mmol/l ( )

10.How would you rank the importance of the following monitoring parameters in sepsis? Use the score format below

(1-Not necessary; 2-Equivocal/lndifferent; 3-Necessary; 4-Mandatory)

	1	2	3	4
Oxygen saturation ($sp0_2$)				
Foley catheter				
Telemetry				
Non-invasive blood pressure (NIBP)				
Intra arterial blood pressure (IABP)				
Central venous pressure (CVP)				
CVP with continuous $scV0_2$				
Pulmonary artery catheter				

*For questions 12 and 13, use the score format below, and mark as appropriate

(1-Never; 2-Rarely; 3-Sometimes; 4-Often; 5-Always)

11. In a patient presenting with septic shock, what type of fluid would you administer in the 1st 6 hours of resuscitation?

	1	2	3	4	5
Normal saline					
Ringers' lactate					
Half-strength Darrows					
5% dextrose					
5% albumin					
Pentastarch					
Hemacael					

12. What end-points would you use to evaluate if a patient is adequately volume resuscitated?

	1	2	3	4	5
Heart rate					
Blood pressure					
Peripheral perfusion					
Urine output					
CVP					
$ScV0_2$					
Cardiac output/ index					

13. During initial fluid resuscitation what would be your target CVP in a mechanically ventilated patient?

$8cmH_20$ ( ) $10cmH_20$ ( ) $12cmH_20$ ( ) $14cmH_20$ ( )

14. If a central venous saturation ($scV0_2$) of 70% is not achieved after fluid resuscitation to target CVP, would you consider transfusion of packed red blood cells to achieve this?

Yes ( ) No ( )

15. What is the lowest haemoglobin trigger that you would use to administer a red blood cell transfusion?

6g/dl ( ) 7g/dl ( ) 8g/dl ( ) 9g/dl ( ) lOg/dl ( )

llg/dl ( ) Others(please specify)

16. If the $scV0_2$ is still below the set goal (< 70%) after above measures, would you consider starting an inotropic agent to further increase oxygen delivery?

Yes ( ) No ( )

17. Which of these agents would you recommend to achieve this?

Dopamine ( ) Epinephrine ( )

Dobutamine ( ) Norepinephrine ( )

18. Empirical intravenous combination antibiotic therapy should be started as soon as possible and within the 1st hour of recognition of septic shock or severe sepsis.

Yes ( ) No ( )

19. De-escalation to the most appropriate single therapy after susceptibility profile is known is recommended.

Yes ( ) No ( )

20. Which 1st choice vasopressor agent do you employ to correct hypotension in septic shock?

Dopamine ( ) Norepinephrine ( )

Epinephrine ( ) Vasopressin ( )

21. Would you recommend a conservative fluid strategy for patients with established ALI/ARDS?

Yes ( ) No ( )

22. Following is a table outlining some of the challenges/ limitations faced in the management of patients with severe sepsis and septic shock. How would you rank each of them using the score format below?

(1- Major; 2- Intermediate; 3- Minor)

	1	2	3
Delay in making definitive diagnosis			
Unavailability of diagnostic tests			
_Delay in getting the lab results to aid management			
Non-applicability of results in management			
Lack of monitoring equipments/ parameters to aid management			
Delay in surgical intervention when needed			
J-ack of pharmacological agent(s) needed in management			
-unavailability			
-expensive			
: Inadequate multi-disciplinary support			
JfnitedCCU bed space			

APPENDIX 3

WORK PLAN

ACTIVITY	2010 July	2010 Sept	2010 Oct	2010 Nov	2010 Dec	2011 Jan	2011 Feb	2011 Mar	2011 Apr	2011 May
Proposal Writing			V	V						
| Proposal ^ Presentation					V					
' Presentation 1 to Ethical I Review 1 Committee					V					
[1] Data Collection										
Data Processing									V	
i Report i Writing									V	
Study ***^mentation***										

APPENDIX 4

BUDGET

Item	Total cost (KShs)
Stationary and printing costs	14,000
Document binding	1,500
Internet hours	1,200
| Phone call costs	1,000
Statistician fee	10,000
iERCfee |	1,000
SUBTOTAL	28,700
10% Contingency	2,870
GRAND TOTAL	31,570

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C S C O

KENYATTA NATIONAL HOSPITAL
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Ref. KNB-ERC/ A/118

13h May 2011

Dr. David Chomba Mwai
Ceptof Surgery
School of Medicine
University o(Nairobi

Dear Dr. Chomba

Research Proposal: "A survey of the practice in the management of severe sepsis and septic shock by Anaesthesia practitioners at the Kenyatta N. Hospital Critical Care Unit" (P54/02/2011)

This is to inform you that the KNH/UON-Ethics & Research Committee has reviewed and approved your above revised research proposal. The approval periods are 13th May 2011 12* May 2012.

You .'/ill be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimens must also be obtained from KNH/UON-Ethics & Research Committee for each batch.

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

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

Yours sincerely.

PROF A N GUANTAI

SECRETARY, KNH/UON-ERC

c c. The Deputy Director CS, KNH
The Dean, School of Medicine, UON
The Chairman, Dept.of Surgery, UON
The HOD, Records, KNH%
Supervisor: Dr. Julius M. Muriithi, Dept.of Surgery, UON