SERUM LACTATE LEVEL - PREDICTOR OF OUTCOME IN PEDIATRIC SEPTIC SHOCK

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CHENNAI

APRIL-2013

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[Dr. C. KARTHIKEYAN]

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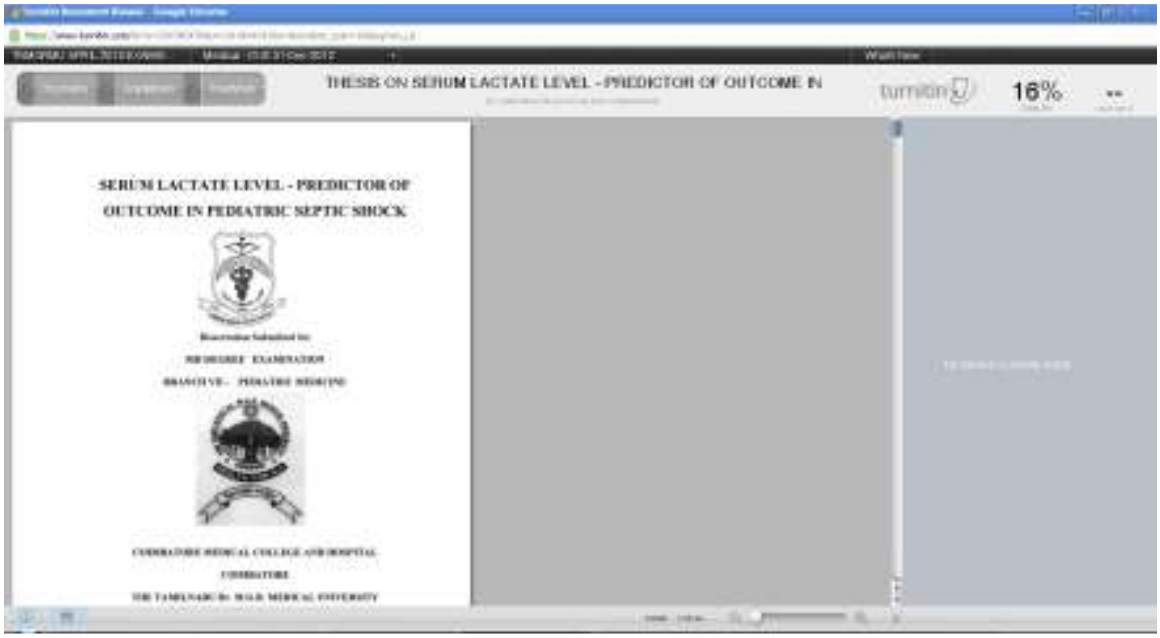
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OUTCOME IN PEDIATRIC SEPTIC SHOCK

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LIST OF ABBREVATIONS

PICU	-	Pediatric Intensive Care Unit
PRISM	-	Pediatric Risk of Mortality
LPS	-	Lipopolysaccharide
TNF	-	Tumour Necrosis Factor
USG	-	Ultrasound
MRI	-	Magnetic Resonance Imaging
MRSA	-	Methicillin Resistant Staphylococcus aureus
CT	-	Computed Tomography
TLR	-	Toll Like Receptor
IL – 1	-	Interleukin - 1

INTRODUCTION

Critical care medicine has remarkably improved in past few decades. Newer antibiotics are being introduced daily. Even then, sepsis is one of the leading causes of death worldwide. Sepsis related deaths are more common in developing nations like India. Epidemiology of sepsis is changing. The reasons for this change are infections which were previously fatal are now controlled by use of effective antibiotics and immunization. Yet new infections are on the rise. Increased utilization of invasive devices and technology has led to health care associated infections. Various biochemical indicators are used to diagnose, prognosticate and to guide treatment in children with septic shock.

OXYGEN DELIVERY

The main function of cardio respiratory system is to maintain delivery of oxygen and nutrients to the body tissues and remove the end products of metabolism. When there is reduced oxygen supply, tissue demands could not be met and this results in low central venous oxygen saturation. Anaerobic metabolism occurs when there is prolonged tissue hypoxia leading to the production of lactic acid. Adequate supply of oxygen to tissues depends on

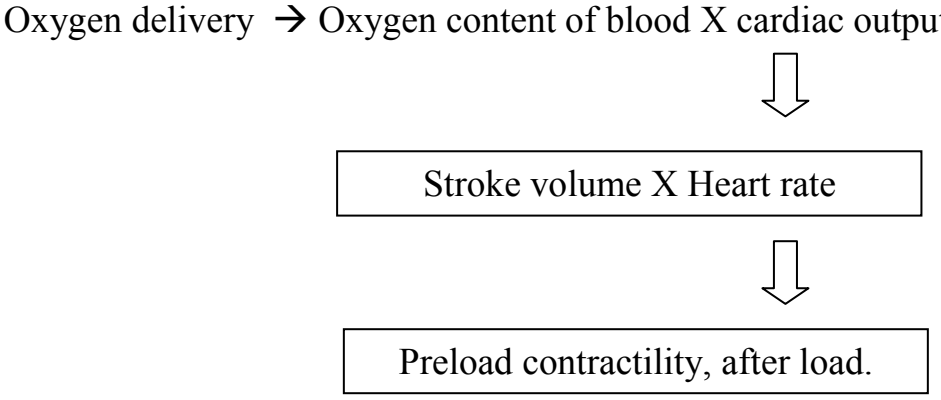
1. Adequate oxygen content in the blood.
2. Cardiac output with sufficient blood flow to organs.

3. Adequate blood flow according to local tissue metabolic demand.
4. Ability to utilize oxygen by the mitochondria

Oxygen content in blood is determined by the concentration of hemoglobin and percentage of hemoglobin that is saturated with oxygen.

Adequate blood flow to the tissues is determined by cardiac output and local tissue demand. Cardiac output is the amount of blood that flows through tissues in 1 minute. Cardiac output is determined by stroke volume and heart rate.

Stroke volume is the amount of blood pumped by the heart with each beat. Heart rate is the number of contractions by heart each minute.



SHOCK

Shock is an acute syndrome characterised by body's inability to deliver adequate oxygen to meet the metabolic demands of vital organs and tissues[1]. In shock there is insufficient oxygen at the tissue level to support

normal aerobic cellular metabolism. If inadequate tissue perfusion persists adverse vascular, inflammatory, metabolic, cellular, endocrine and systemic responses worsen physiological stability.

Compensation for inadequate oxygen delivery involves various responses that attempt to preserve oxygenation to vital organs like brain, heart, kidney, liver at the expense of other organs. Untreated shock causes irreversible tissue and organ injury ultimately leading to death. The pattern of responses, pathophysiology, clinical manifestation and treatment vary significantly depending on the specific aetiology, clinical circumstances and individual response to the shock states.

There are 5 types of shock

(1) Hypovolemic shock (2) Cardiogenic shock (3) Obstructive shock

(4) Distributive shock (5) Septic shock

HYPOVOLEMIC SHOCK

This is the most common type of shock in children worldwide. It is characterised by decreased preload secondary to internal or external loss. Causes include haemorrhage, burns, vomiting and diarrhoea.

CARDIOGENIC SHOCK

It occurs secondary to poor myocardial function. Causes include congenital heart disease, cardiomyopathy, ischemia to myocardium, arrhythmias.

OBSTRUCTIVE SHOCK

It occurs due to decreased cardiac output secondary to direct impediment to outflow or restriction of pumping of all cardiac chambers. Aetiologies include tension pneumothorax, pericardial tamponade, pulmonary embolism, anterior mediastinal masses and critical coarctation of aorta.

DISTRIBUTIVE SHOCK

In distributive shock abnormalities of vasomotor tone occur due to loss of venous and arterial capacitance leading to maldistribution of fluid. Causes include anaphylaxis, loss of sympathetic vascular tone secondary to spinal cord or brainstem injury.

SEPTIC SHOCK

Sepsis is a clinical syndrome that occurs as a result of severe infection. It is characterized by systemic inflammation and widespread tissue injury. Septic shock involves complex interaction of distributive, hypovolemic and cardiogenic shock. There is third spacing of fluids into the

interstitium causing hypovolemia. Inappropriate vasodilatation occurs leading to maldistribution.

HISTORY OF SEPSIS

The word 'sepsis' was first introduced by Hippocrates[2] (460 - 370 BC). It was derived from the Greek word 'Sipsi' which means "make rotten". Ibn Sina (979 – 1037 BC) found the coincidence of blood putrefaction and fever[2]. Ignaz Semmelweis (1818 - 1865), an obstetrician gave the modern view of sepsis. He discovered that puerperal fever was caused by decomposed animal matter that entered the blood system. He demonstrated that, hygienic measures like hand washing before examination can reduce the occurrence of puerperal fever. Joseph Lister introduced antisepsis. Louis Pasteur, a French chemist discovered tiny single cell organisms. He named them as bacteria and said that these microbes could be causing disease[2]. Even after many years of discovery, sepsis continues to be the major cause of morbidity and mortality.

EPIDEMIOLOGY

According to data from the World Health Organization, United Nations Children's Fund, 70% of Under 5 mortality in children is caused by infections[3]. Studies show that more than 40,000 children develop severe sepsis each year in United States with an annual incidence of 0.56 cases per

1000 population[4]. Many experts say that the incidence of sepsis will continue to increase by approximately 1.5 % every year. While above are the problems in developed nations, in developing countries other difficulties faced include poverty, overcrowding, illiteracy, poor funding for health care.

PATHOPHYSIOLOGY

Pathophysiology of septic shock is very complex. It involves a cascade of events ranging from bacteremia to sepsis, severe sepsis and septic shock. It depends on the specific microorganism, immune status of the host and other factors such as presence of indwelling catheter. The first step in pathogenesis is the colonization and invasion. Encapsulated organisms like Pneumococcus, Hemophilus influenzae (H.influenzae) normally reside in the nasopharynx. A preceding viral upper respiratory tract infection causes alterations in local host defence mechanism resulting in bacteraemia. For example, cytokines generated during viral infection causes up regulation of platelet activating factors on epithelial cells of the respiratory system. Pneumococci bind to these receptors and invade subsequently. In case of gram negative enteric organism, pili or adhesin helps in attachment to the epithelial surface. Similarly, pili are also important in the pathogenesis of

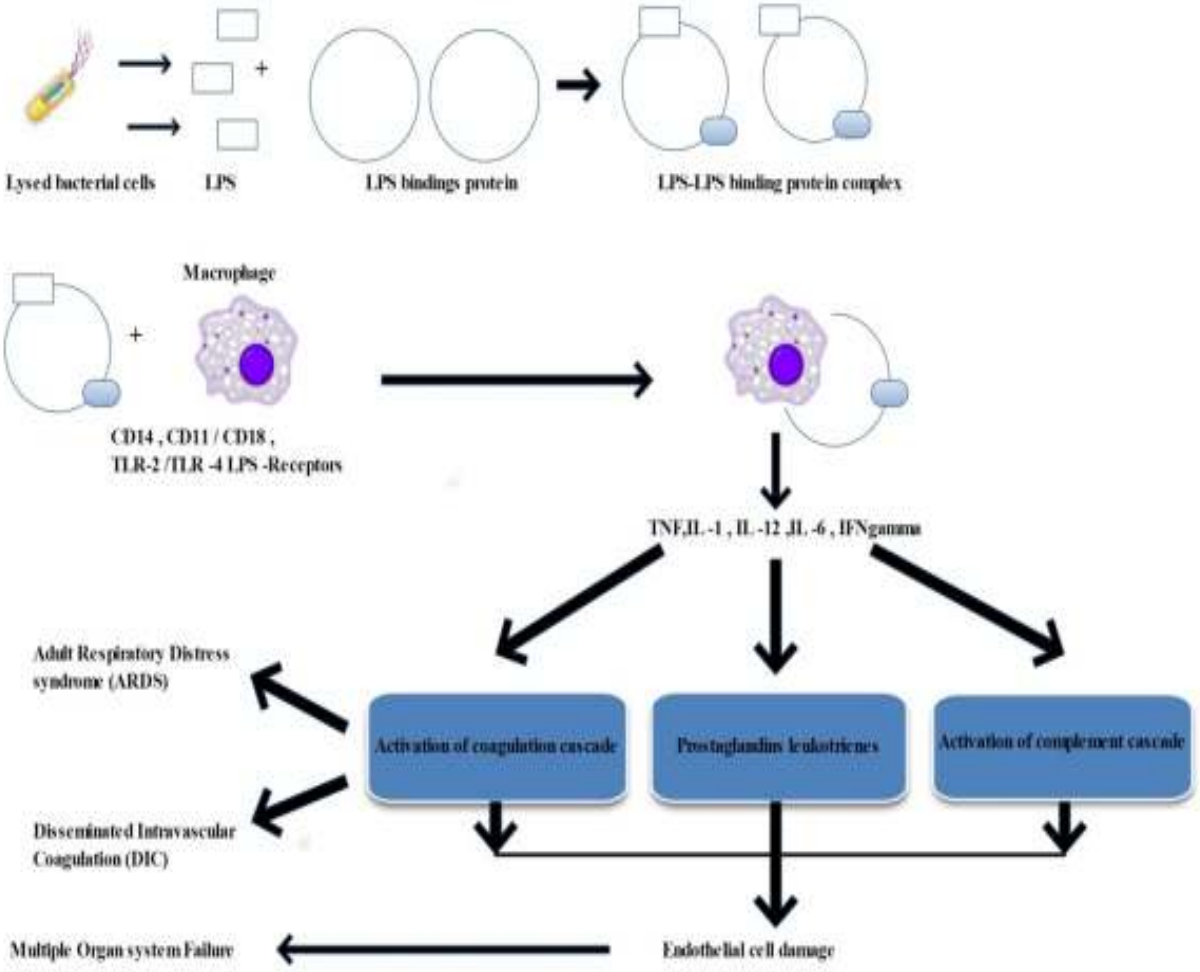
some gram positive bacterial infections like Streptococcus pyogenes, Group B streptococcus, and Streptococcus pneumoniae.

Gram negative organisms are responsible for bacteraemia from gastrointestinal and genitourinary system. These bacteria cause localized abscess or peritonitis leading to bacteraemia. In some children these organisms translocate from intestine into blood stream, when the mucosa is damaged. The integrity of skin protects against invasion by microorganisms like Staphylococcus aureus, Streptococcus which are common inhabitants. Any ulcer in skin or presence of foreign material within the skin like catheters renders the skin more susceptible to bacterial invasion.

The endotoxin or Lipopolysaccharide has three basic components

1. Terminal side chain consisting of repeating oligosaccharides These are responsible for the antigenic specificity of 'O' antigens and are unique to a particular strain
2. Core lipopolysaccharide
3. Lipid A – It is similar among different strains. It is responsible for biological activity of endotoxin.

FIG 1: PATHOGENESIS OF SEPTIC SHOCK

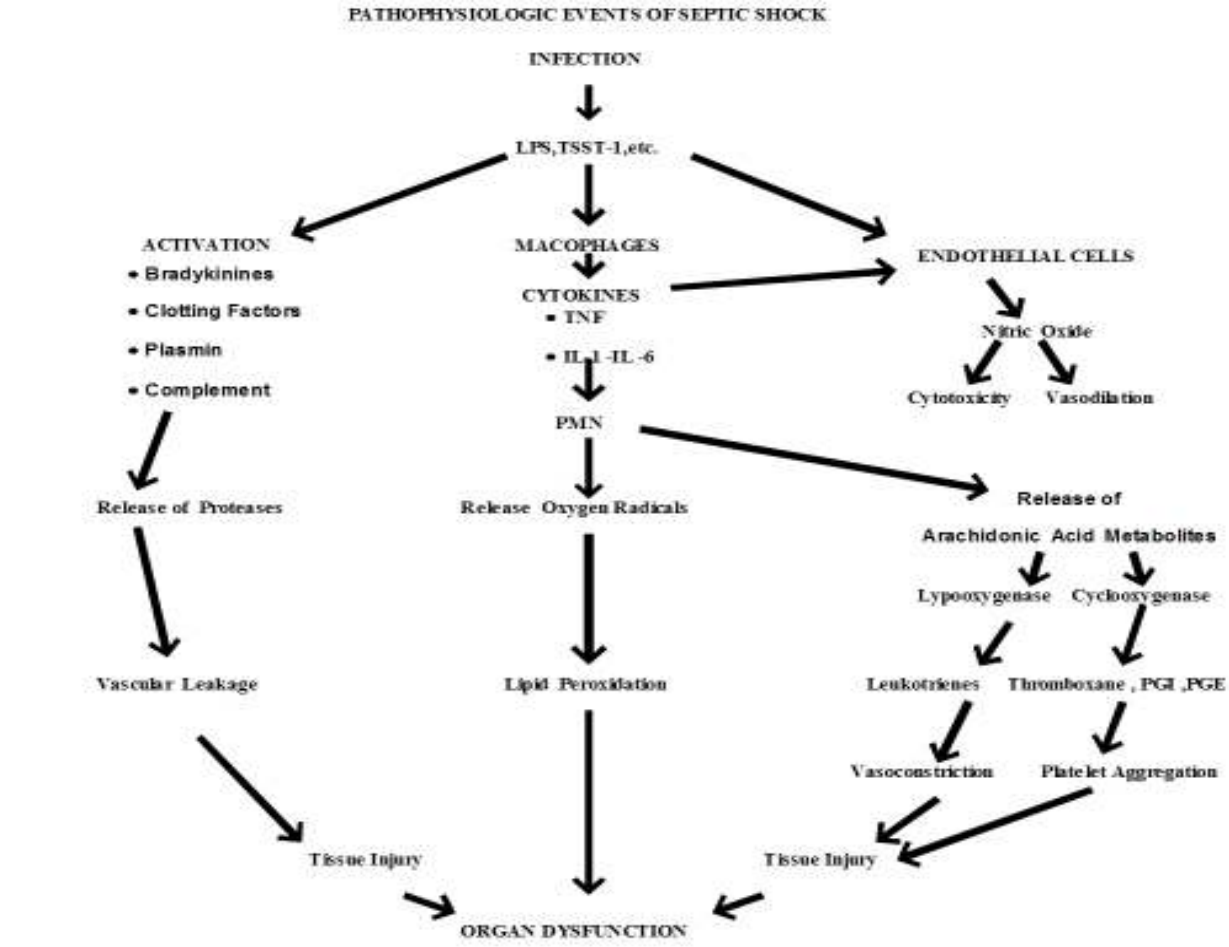


The biological equivalent of endotoxins in gram positive bacteria is the peptidoglycan layer as well as non-peptide glycan polymer teichoic acid. Some exotoxins of gram positive organisms initiate inflammation. Examples include toxic shock syndrome toxin from certain strains of Staphylococcus aureus and certain strains of group–A Streptococcus. These toxins act as

super antigens that bind to non – conventional binding sites on antigen-presenting cells and T-cells. This type of attachment permits very small amount of toxins to stimulate proliferations of large number of T lymphocytes and subsequently large quantities of cytokines.

The LPS-binding protein is an acute phase protein which helps in recognition of endotoxin. This protein binds with LPS and then forms a complex with receptor for LPS, CD14 molecule[5,6]. This CD14 is present on surface of macrophage. This complex then activates trans membrane signaling pathways involving toll-like receptors [TLR- 4 for gram negative bacteria; TLR 2 for gram positive bacteria] which in turn causes activation of various enzymes. This leads to translocation of nuclear factor KB and production of tumor necrosis factor and various inflammatory mediators.

FIG 2: PATHOPHYSIOLOGICAL EVENTS OF SEPTIC SHOCK



The major pathophysiologic events in sepsis are depicted. Endotoxin or Exotoxin activates factors and cells, mainly macrophages and endothelial cells leading to release of endogenous mediators and organ dysfunction

Endotoxin has a variety of effects

1. Activation of endothelium
2. Activation of macrophage

Endotoxin causes release of endothelium derived relaxing factors or nitric oxide which is a potent vasodilator and causes hemodynamic disturbance. Coagulation cascade is activated. Both the extrinsic and

intrinsic pathways are activated. Tissue factor released from endothelium initiates the extrinsic pathway with subsequent activation of factor VII, X and thrombin. Interaction of endotoxin with endothelium causes activation of factor XII (Hageman factor) which in turn initiates intrinsic clotting pathway. In sepsis, levels of Protein – C are decreased. Protein – C has antithrombotic and anti-inflammatory properties.

The lipopolysaccharide activates complement cascade by the classic or alternate pathway. Activated factor XII triggers complement system to produce C_{5a}, which is a chemotactic stimulus for neutrophils causing neutrophil aggregation. These in turn produce reactive oxygen species which cause cell injury, lipid peroxidation and DNA strand breaks. LPS or by complement system, activate phospholipase enzymes resulting in release of arachidonic acid from cell membrane phospholipids.

LPS – LPS binding proteins complex binds to CD14 antigen on surface of macrophages and results in release of various inflammatory mediators particularly tumour necrosis factor and interleukin-1. TNF is one of the central mediators in pathogenesis of septic shock because it is responsible for various biological effects like fever, shock, myocardial depression, coagulation abnormalities, capillary leak and metabolic changes[7,8,9,10]. Interleukin – 1 causes fever by increasing prostaglandin E2

release in anterior hypothalamus. Platelet activating factor, another inflammatory mediator is released from activated macrophages. This factor is also produced by platelets and neutrophils. It stimulates cell adhesion and amplifies the action of cytokines.

The factors which determine progression of sepsis to frank septic shock is not well understood. Two key factors are change in intravascular volume and myocardial dysfunction. Most of the inflammatory mediators like arachidonic acid metabolites, cytokines alter the capillary permeability leading to decrease in effective circulating volume. Depression of myocardial function is seen in children with septic shock. These patients have reduced ejection fraction, left ventricular dilatation and altered ventricular performance[11]. TNF and IL-1β are possibly the factors involved in myocardial depression. The inflammatory mediators alter perfusion in microcirculation causing increase in interstitial fluid. This affects the cellular oxygenation and metabolism causing tissue hypoxia. As the tissue hypoxia progresses, anaerobic glycolysis, metabolic acidosis and cell injury ensues leading to cell death and organ failure.

CLINICAL FEATURES

Full blown picture of septic shock is easily identified but early diagnosis is really challenging. It requires high index of suspicion and

knowledge about the disease. Early signs of septic shock are subtle and easily missed. Examination will reveal

1. Mental Status

   Altered mental status is one of the most important signs of shock. Restlessness, inconsolability, anxiousness, agitation, increased drowsiness must be noted.

2. Skin

   We should look for signs of poor peripheral perfusion like cold extremities, mottling, cyanosis. Temperature abnormalities such as hyper or hypothermia must be noted; any evidence of coagulopathy should be noted.

3. Cardiovascular system

   Due to stress various autonomic disturbances occur, of which tachycardia occurs early. Cardiac output is a product of stroke volume and heart rate. In children, cardiac output is mainly increased by increase in heart rate rather than stroke volume. Fall in blood pressure occurs late leading to decompensated state. In warm phase of septic shock, due to vasodilatation, there will be wide pulse pressure, bounding peripheral pulses, flash capillary refill. In cold phase, there will be tachycardia, cold extremities, weak peripheral pulses and

prolonged capillary refill time (>3 seconds). Warm shock if not recognized early or if untreated will eventually result in cold shock.

4. Respiratory system

Respiratory rate is increased as a result of compensation to metabolic acidosis. Uncorrected shock can lead to development of acute respiratory distress syndrome characterized by the progressive worsening of respiratory distress which manifests as tachypnoea, nasal flaring, intercostal, supra sternal and subcostal retractions with bilateral rales on auscultation.

5. Urine output

Decreased urine output occurs. In later stage it can lead to renal failure.

INVESTIGATIONS

Complete blood count – will reveal anemia, leucocytosis, and thrombocytopenia. Peripheral smear will show neutrophilic leucocytosis with shift to left, toxic granules, Dohle bodies. Leucopenia and neutropenia are observed in case of overwhelming sepsis. Other hematologic abnormalities are prolonged prothrombin and partial thromboplastin times, decreased serum fibrinogen, elevation of fibrin split products in case of disseminated intravascular coagulation. Other abnormalities which can occur

are hyperglycemia or hypoglycemia, hypocalcemia, hypoalbuminemia. Blood gas analysis reveals high anion gap with metabolic acidosis. Acute phase reactants like C - reactive protein, erythrocyte sedimentation rate will be elevated. Blood culture and other appropriate cultures are necessary to identify the organism.

MANAGEMENT

Management of septic shock is complex

It involves

1. Emergency Resuscitation
2. Timely initiation of antimicrobial therapy
3. Source Control
4. Goal directed therapy for organ dysfunction

1. Emergency Resuscitation[12]

Emergency management include rapid cardiopulmonary assessment, careful and repeated physical examination.

Golden hour of management

0-5 min:

1. By rapid cardiopulmonary assessment, recognize altered mental status and altered perfusion.

2. Administration of 100 % high flow oxygen is crucial. Venturi mask or non-rebreathing mask can be used for administering high flow oxygen.
3. Establishment of intravenous access. If emergency intravenous access cannot be obtained, intraosseous access should be obtained. If airway is unstable or the patient is drowsy and unresponsive, Bag and Mask ventilation with 100 % oxygen should be started with plan for intubation and mechanical ventilation should be done. Other indications for intubation are

    a) Hypotension on arrival or during treatment

    b) Persistently low Glasgow coma scale score of less than eight

    c) Convulsions not controlled even with two doses of benzodiazepines and with signs of raised intracranial tension.

5-40 min:

Fluid boluses with isotonic crystalloid of 20 ml/kg should be given over 20 minutes if blood pressure is normal; if there is hypotension, boluses should be given as rapidly as possible and up to 60 ml/ kg should be administered to achieve therapeutic end goal. During and after each bolus, assess for signs of fluid overload in the form of frothy secretions, rales, new

onset of signs of respiratory distress, hepatomegaly. In case of warm septic shock, shock due to gastrointestinal sepsis, fluid as much as 200 ml/kg may be required in the initial few hours. In malnourished children, administering rapid fluid bolus can cause fluid overload, so rate and volume of fluid should be slow and carefully titrated.

40 – 60 min:

Shock not responding even after adequate intravascular volume repletion requires vaso active drugs. In children with fluid refractory hypotensive shock with low systemic vascular resistance, dopamine is the 1st line drug. Children with septic shock often have low cardiac output and myocardial dysfunction. So dopamine with or without dobutamine should be used.

Dopamine:

It is a natural precursor of epinephrine and non-epinephrine. It is usually the inotrope of choice in septic shock. It possesses dose dependent effects. At low doses (1 - 5 μg/kg/min), its action is predominant on dopamine receptors resulting in selective vasodilatation in splanchnic, renal and coronary vessels. At moderate doses (5 – 15 μg/kg/min) it acts on β_1– adrenergic receptors causing increase in heart rate and myocardial

contractility. At doses (15 – 25 μ/kg /min) it causes arterial vasoconstriction by acting on α_1 receptors.

Dobutamine:

It is a β1 and β_2 adrenergic agonist. It increases cardiac contractility (1 - 20 μg/kg/min) with little effect on heart rate. Dobutamine causes after load reduction and is useful in cardiogenic shock. In septic shock, it should be used in combination with other vasopressors, because dobutamine can cause peripheral vasodilatation leading to hypotension.

Adrenaline:

It is a potent β1 adrenergic agonist. Also has α1 and β2 adrenergic effect. Causes increase in heart rate, contractility. Used in doses of 0.1 – 1 μg/kg/min adrenaline is a potent vasoconstrictor. Nor adrenaline increases blood pressure by increasing systemic vascular resistance.

Vasopressin:

It is a natural hormone which causes vasoconstriction by acting on V1 receptors. In sepsis Vasopressin stores are depleted and there is also down regulation of Vasopressin receptors. Infusion of low doses of Vasopressin helps in improving blood pressure[13]. Side effects include skin necrosis, intestinal ischemia and decreased cardiac output as a result of increased after

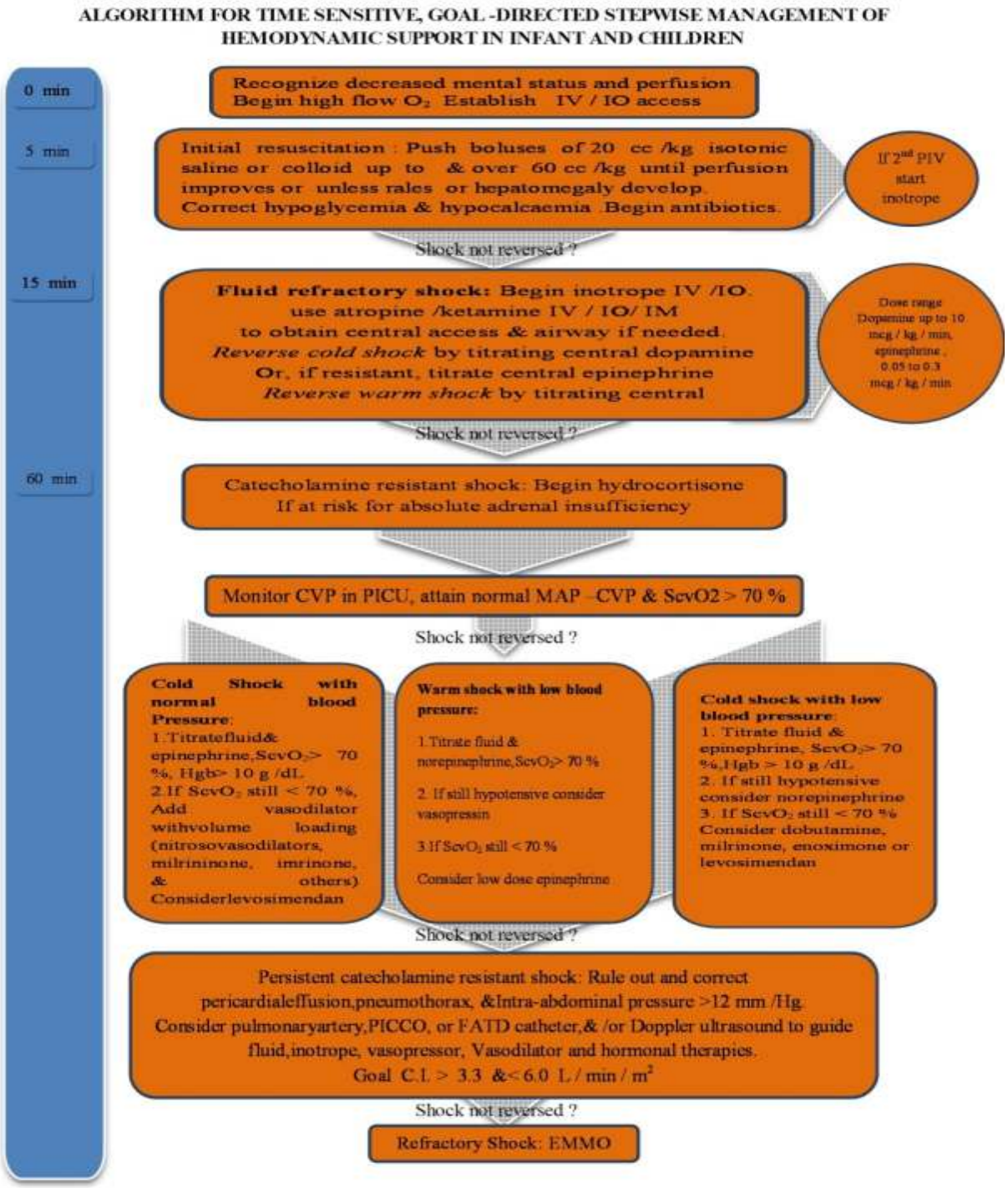
load. So Vasopressin is reserved for patients with significant vasodilatory shock.

Milrinone:

It is a phosphodiesterase type 3 inhibitor. This enzyme causes degradation of intra cellular cyclic AMP. Blockade of this enzyme cause elevated levels of cyclic AMP which leads to improved contractility of heart and relaxation. In peripheral vessels it causes vaso dilatation. Useful in children with normotensive, catecholamine resistant shock with low pulse pressure and increased systemic vascular resistance. Milrinone has longer elimination half-life and cause hypotension. So careful monitoring of blood pressure is important.

FIGURE 3:

Goal – Directed Step wise Management[14].



Beyond one hour:

Fluid refractory, dopamine, dobutamine resistant shock – shock not corrected even dopamine and or dobutamine infusion. These children require close monitoring in intensive care unit with Central venous pressure, mean arterial pressure, echocardiography. Further treatment should be based on CVP, echocardiography for titrating fluids and inotropes.

Blood and component therapy

The appropriate haemoglobin (Hb) in children with severe sepsis is debatable. Studies in children with septic shock are limited. Based on adult studies Hb level of 10g/dl during resuscitation is recommended.

Fresh Frozen plasma

Unnecessary use of Fresh frozen plasma exposes children to hazards of transfusions. It is indicated only in patients with coagulation abnormality and is bleeding actively. Also just before surgery or invasive procedures.

Acid base and electrolyte abnormalities

In sepsis, there is increased catabolism and increased requirement of glucose. So children are prone for hypoglycemia. Blood sugar should be monitored and hypoglycemia must be treated. Ionised calcium levels are commonly low in children with septic shock (< 4.5 mq/l). This leads to myocardial dysfunction should be corrected by i.v. Calcium.

2. **Timely initiation of antimicrobial therapy**

Antibiotics should be administered within the 1st hour preferably after obtaining appropriate culture. Early and appropriate antimicrobial therapy is one of the corner stone's in treatment. Timely antimicrobial therapy determines outcome. Empirical antibiotics administered should be broad spectrum covering common offenders in the particular age group. In neonates, most common pathogens are group B streptococci, gram negative enteric bacteria and Listeria monocytogenes. In infants and children beyond neonatal period Streptococcus pneumoniae, Hemophilus influenza is a common organism.

Empirical therapy for neonates is a combination of third generation, cephalosporin and aminoglycoside. For Infant and children, third generation, cephalosporin is the initial choice[1].

Penicillin resistant pneumococci, community or hospital acquired MRSA - vancomycin should be added to empiric therapy.

Intra- abdominal condition - antibiotic covering anaerobes like metronidazole, clindamycin or piperacillin – tazobactum must be added

Clinical suspicion of herpes simplex infection - acyclovir

Hospital acquired sepsis - 3rd or 4th generation Cephalosporin or Piperacillin – tazobactum with an aminoglycoside. Empiric antifungal therapy should be considered in patients with immunosuppression.

The recommendations for antimicrobial therapy are broad, generalised. Therapy must be modified according to clinical situation and local resistance pattern. Further treatment should be guided based on culture and sensitivity results.

3. Source control

Source of sepsis should be sought. This should go hand in hand with resuscitation. Example incision and draining of abscess, debridement of necrotic tissue, removal of infected device.

4. Goal directed therapy for organ dysfunction

Cardiovascular system dysfunction

Children with septic shock and myocardial dysfunction are difficult to manage. These children should be treated cautiously with small volume usually 5 ml/kg fluid boluses and early inotropes. Beyond the 1st hour, stabilization of cardiovascular system should be directed to achieving normal mixed venous oxygen saturation. Normally oxygen delivery exceeds oxygen consumption by threefold. The oxygen extraction ratio is about 25%. Normal SVO_2 (Mixed Venous Oxygen Saturation) is 75 to 80%. A

decreasing SVO_2 implies increasing oxygen extraction ratio and decrease in oxygen delivery to tissues. A normal SVO_2 indicates adequate oxygen delivery at cellular level[1].

Nor adrenaline and more fluids are useful in children with persistent warm shock. In children with Nor-adrenaline resistant shock, Vasopressin is found to be useful. Vasopressin can overcome alpha receptor desensitization and improve vascular tone. Children with cold shock and normal blood pressure improve with fluid and decreasing after load. The phosphodiesterase type III inhibitors like milrinone can overcome β – adrenergic desensitization. In those children with cold shock and hypotension, treatment is difficult. They can be treated with more fluids and adrenaline.

Respiratory system dysfunction

In children with acute respiratory distress syndrome, goal is to treat hypoxia and respiratory acidosis. These children have respiratory muscle fatigue. So early endotracheal intubation and ventilation should be performed. During mechanical ventilation, lung – protection strategies should be adopted to reduce ventilator induced lung injury. This is because volutrauma and barotraumas can lead to disruption of alveolar and capillary endothelial tight junctions. This causes exudation of fluid and protein in

alveoli which in turn attract inflammatory cells. The cytokines and inflammatory mediators exacerbate the injury decrease surfactant production further impairing gas exchange. Avoidance of tidal volume ≥ 10 ml/kg and plateau pressure ≥ 30cm H_2O decrease alveolar damage[1]. Provision of adequate positive end expiratory pressure is another strategy. Inappropriate PEEP can lead to atelectrauma. Also maintaining an adequate PEEP, helps in decreasing inspired oxygen concentration which in turn limits occurrence of oxytrauma. Ventilator associated pneumonia can be prevented by elevation of head of the bed to 30 degrees and effective oral, endotracheal suctioning.

Gastrointestinal dysfunction

In shock, there is reduced blood flow to gastrointestinal system. Decreased splanchnic perfusion causes mucosal barrier dysfunction and can lead to translocation of bacteria and endotoxin into blood stream. Children with sepsis are at increased risk of malnutrition

This is because

1. Protein energy malnutrition is commonly found in children with sepsis. This is a main problem particularly in countries like India
2. Child with illness often has reduced appetite.

3. In sepsis metabolic demand is increased due to fever, tissue catabolism

Provision of adequate nutrition support is very important. Whenever possible, enteral feeding is better than total parenteral nutrition. Improved survival and decreased hospital stay has been observed in critical ill patients with use of early enteral feeds

Endocrine Dysfunction:

1. Disturbance in glucose metabolism occurs more often in children with sepsis. Both hypo and hyperglycemia can occur. Hypoglycemia occurs more commonly in neonates and its consequence can be devastating. Similarly hyperglycemia is also harmful. There is increased risk of infection and delayed wound healing due to impaired neutrophil function, can occur. Insulin can be used to control hyperglycemia but may lead to hypoglycemia.
2. Adrenal insufficiency can occur in children with sepsis. The role of corticosteroid therapy in children with septic shock has been extensively investigated. Stress doses of hydrocortisone 50 mg /m^2 / dose should be used in children with fluid refractory, catecholamine resistant shock.

Renal dysfunction:

Acute renal failure is a common complication in patients with sepsis. These patients pose additional problems because of difficulty in fluid management and dysfunction in clearance of toxins. Administration of continuous renal replacement therapy is useful in sepsis. The advantages are

1. Removal of toxins and harmful mediators
2. Adequate calories can be provided without exacerbating fluid overload.

Pneumonia:

Pneumonia is an important cause of mortality in children under 5 years in developing countries. Causative organisms vary according to age, host and environmental factors.

Causes:

1**.** Bacterial

In New-borns

Group –B Streptococci

E.Coli

Klebsiella

Listeria monoytogenes

Staphylococcus aureus

In Older children

Streptococcus pneumoniae

H.Influenzae

Staphylococcus aureus

2. Non-bacterial

Rickettsia

Pneumocystis jiroveci

Viruses

Respiratory synctial virus, Cytomegalovirus, Herpes simplex virus, Epstein – Barr virus, Human metapneumovirus, adenovirus, rhinovirus, enterovirus.

Important factors in development of bacterial pneumonia are virulence of the pathogen, absence of specific humoral immunity and presence of viral upper respiratory tract infection. Most pneumonia is the result of colonization of nasopharynx followed by aspiration or inhalation. Viral infection causes destruction of respiratory epithelium or up regulation of bacterial adhesion molecules.

Clinical features:

In young infants, fever, chills, rigors, restlessness, poor feeding, gastrointestinal complaints, difficulty in breathing occurs. In new-born

episodes of apnoea, cyanosis, bradycardia can occur. On examination, signs include tachypnoea, dyspnoea, grunting, added sounds. Abdomen distension may result from paralytic ileus or swallowed air.

Acute non-bacterial pneumonia are characterised by coryza, low grade fever, decreased appetite. Dehydration can occur because of fever, hyperventilation and decreased intake. On auscultation fine crackles may be present. Wheezing may occur when there is associated bronchospasm. Cyanosis in older children is an ominous sign.

Diagnosis:

WBC count is increased. Counts >15,000 /cu.mm is commonly seen in bacterial pneumonia. Leucocytosis is also seen in influenza and Para influenza infection. Counts < 5000 /cu.mm are associated with severe overwhelming infection. Elevated acute phase reactants are seen. Chest x-ray findings in bacterial pneumonia are lobar consolidation, pleural effusion, and pneumatoceles. In non-bacterial pneumonias, usually air trapping, perihilar infiltrates occur. Patchy areas of consolidation indicate lobular atelectasis. X –ray findings do not correlate with clinical findings in most situations.

Gram stain, culture of sputum helps in identifying causative organism. Other specimens include nasopharyngeal secretions, tracheal aspirations, and

bronchoalveolar lavages. Polymerase chain reaction for pneumococcus. Polysaccharide antigen in urine for pneumococci, H.Influenzae

Treatment:

Treatment of pneumonia involves specific therapy and supportive measures. In case of non – bacterial pneumonia therapy is primarily expectant and supportive. Administration of warm, humidified oxygen correction of dehydration and monitoring is necessary.

In case of fulminant varicella zoster pneumonia, therapy with acyclovir is indicated. Progressive Cytomegalovirus interstitial pneumonia is treated with ganciclovir and immunoglobulin. Epidemics of influenza are treated with oseltamivir. Pneumocystis jiroveci pneumonia is treated with Cotrimoxazole or Pentamidine. Inhaled Ribavirin is useful in treating Respiratory syncitial virus pneumonia.

Meningitis:

Meningitis is inflammation of meninges. Even though antibiotic therapy has improved prognosis in meningitis; it still continues to be an important cause for morbidity and mortality.

Causes:

In New born

Gram negative enteric organisms are most common.

In infants and children

H.Influenzae, Streptococcus pneumoniae and Staphylococcus aureus.

Pathogenesis:

Most cases of bacterial meningitis infect the meninges by following steps

i. Colonization of upper respiratory tract

ii. Invasion of blood from respiratory focus

iii. Seeding of meninges and then inflammations

Less commonly, lepto meningeal inflammation can result from contiguous spread or hematogenous dissemination from a remote site.

Once in the blood stream, the common pathogens are capable of evading host immune responses the capsular polysaccharides inhibit neutrophil phagocytosis and complement system. The specific pathophysiological changes are due to bacterial products and the inflammatory response of the host to those products. TNF – α and IL -1 Once in the blood stream, the common pathogens are capable of evading host immune responses the capsular polysaccharides inhibit neutrophil phagocytosis and complement system. The specific pathophysiological changes are due to bacterial products and the inflammatory response of the

host to those products.TNF – α and IL -1 are key mediators in initiation of meningeal inflammation. These cytokines activate adhesion molecules attract neutrophils, activate complement system.

Clinical features:

Children usually present with nausea, vomiting, lethargy or irritability, headache, bulging fontanels. Neck rigidity, photopobia, seizures, hemiparesis, transient or permanent cranial nerve palsies may be presenting feature. Kernigs and Brudzinski signs are result of irritation of inflammed sensory nerves. These signs are minimal in infancy

Diagnosis:

Lumbar puncture and CSF analysis must be done as early as possible unless specific contraindications are present. Gross examination of CSF, pressure, microscopic examination for cells, gram stain, biochemical analysis, culture and sensitivity should be done. In children older than 3 months, presence of polymorpho nuclear leucocyte is abnormal. Proteins will be elevated (100 – 500 mg/dl) and sugar will be decreased (< 40 mg/dl). Latex particle agglutination for polysaccharide antigens can be done. Polymerase chain reaction analysis of CSF can be used to detect microbial DNA. CSF –lactate and lactate dehydrogenase will be increased. pH will be decreased. CT and MRI brain are helpful in detection of ventricular

dilatation, presence of infarcts, subdural effusion, and meningeal inflammation.

Treatment:

Third generation cephalosporins – Cefotaxime in the dose of 225 to 300 mg/kg/day or Ceftriaxone 100 mg/kg/day along with Vancomycin 60 mg/kg/day is an appropriate empirical therapy. Vancomycin is recommended in addition because of the increased frequency of Penicillin and Cephalosporin resistant pneumococci. Ceftazidime is efficacious in the treatment of meningitis due to Pseudomonas.

Corticosteroids - dexamethasone 0.15 mg/kg/dose 6th hourly for 2 days is recommended as an adjunct therapy in bacterial meningitis because

1. They decrease intracranial pressure
2. Reduce meningeal inflammation by acting on cytokines
3. Decrease the incidence of sensorineural hearing loss[15,16]

Other supportive therapies include agents to reduce intracranial pressure, fluid restriction in case of SIADH (Syndrome of Inappropriate Anti Diuretic Hormone secretion), control of seizures, management of nutrition electrolyte imbalances.

Urosepsis:

Urinary tract infections are an important cause of fever without focus in young children. Acute pyelonephritis can present as septicemia

Causative organisms:

Escherichia coli – the most common

Klebsiella

Proteus

Enterobacter

Serratia

Pseudomonas

Rare causes include Staphylococcus aureus, Hemophilus influenzae and Streptococcus pneumoniae.

Clinical features:

In neonates, UTIs present as late onset sepsis. In infants and young children they may present as fever with chills and rigor, irritability, poor feeding, back pain, vomiting, loose stools, and oliguria. Lower urinary tract symptoms may or may not be present. On examination dehydration, renal angle tenderness may be present.

Diagnosis:

Examination of urine reveals pyuria. Microscopic hematuria, proteinuria can be present in some cases. Urine dipstick can be positive for leucocyte estrase, nitrite. Significant bacteriuria is defined as $> 10^5$ CFU / ml in clean catched mid – stream urine sample ; In catheter specimens $> 5 \times 10^4$ CFU / ml is significant and any colony count in urine obtained by supra pubic aspiration is significant.

1) The growth of organism in urine culture is necessary for diagnosis
2) Renal scintigraphy with Tc 99m DMSA is the most reliable method for detecting acute pyelonephritis which will reveal decreased uptake in affected areas
3) An USG abdomen examination is useful to detect associated anomalies.

Treatment:

Second or third generation cephalosporin for 7 - 10 days is effective in most of the cases.

Gastro intestinal infections:

Gastrointestinal infections causing septicemia usually result from gastro enteritis and intra abdominal abscesses.

Etiology of gastroenteritis:

The common bacteria causing gastroenteritis are Escherichia coli, Shigella, Salmonella, Vibrio cholera, Clostridium, Campylobacter, Yersinia enterocolitica and Aeromonas hydrophila.

The common bacteria causing intra abdominal abscesses are Enterobacteriaceae, Bacteroides and Peptostreptococcus. Intra-abdominal abscesses are classified as intraperitoneal, visceral and retro peritoneal. Most common are intraperitoneal abscesses associated with appendicitis and trauma. Visceral abscesses occur commonly in liver, pancreas and spleen.

Clinical features:

Fever, malaise, vomiting, loose stools – watery or mixed with blood and mucus, abdominal pain. Dehydration can occur as a result of excessive fluid loss.

Diagnosis:

History, stool examination – microscopy for faecal leucocytes, RBCS. Presence of faecal leucocytes indicates that a patient has colitis. Stool culture for gram negative enterobacteriaceae should be done. In case where Vibrio cholera, Yersinia, Clostridium and Listeria are suspected, special media are needed.

Treatment:

Fluid, electrolyte and nutritional support are very essential. Most infections are self-limited. Third generation Cephalosporins or Co-trimoxazole or Fluoro quinolones are effective in most cases. In cases of sepsis associated with Campylobacteria or Yersinia aminoglycosides are alternatives.

INTRA ABDOMINAL ABSCESS

Clinical features:

Fever, abdominal pain and tenderness over affected area are presenting feature in case of abscess. The symptoms are non-specific like fever, nausea, anorexia, vomiting. Other less common manifestations are hepatomegaly, jaundice, abdominal pain, and abdominal distension. Subphrenic abscesses present with respiratory symptoms and referred pain. Splenic abscess present with tender splenomegaly. Retroperitoneal infections present with fever, pain in hip and back, limping in case of ileopsoas abscess.

Diagnosis:

Plain X-rays show extra intestinal air fluid level, localized ileus in case of pelvic abscess and elevated diaphragm, right pleural effusion in case of liver abscess.

USG abdomen can detect abscess. CT with contrast enhancement is the most sensitive tool for detecting intra-abdominal abscesses. Extent of involvement and good anatomic resolution is possible. Abscess fluid is seen as areas of low attenuation with enhancing rim. Leucocytosis, elevated acute phase reactants, blood cultures may be helpful.

Treatment:

Surgical drainage either open or percutaneous under CT or USG guidance is often required. Empirical therapy with antibiotics covering Enterobactericeae, anaerobes should be administered. In case of liver abscess, anti-Staphylococcal agents should be added. Previously Ampicillin + Metronidazole + 3rdgeneration Cephalosporin was used. β – lactamase inhibitors combinations such as Piperacillin - tazobactum with an aminoglycoside are also effective. Monotherapy with carbapenams are cost effective alternative. Duration of therapy should be minimum 4 weeks.

Musculo skeletal infections:

This includes osteomyelitis, septic arthritis, and myositis. Osteomyelitis occurs more common in 1st two decades of life. The micro-organism reaches bone in three ways.

1. Direct inoculation usually traumatic
2. Local invasion from nearby focus
3. Hematogenous

Etiology:

Bacterial infections are most common

Staphylococcus aureus

Group A streptococcus

H.Influenzae

Kingella kingae

Streptococcus pneumoniae

In neonates,

Gram negative organism

Group – B streptococcus

Puncture wound osteomyelitis - Pseudomonas

Clinical features:

Newborn - irritability, pseudoparalysis, fever, refusal of feeds and others features of septicemia. Infants and young children – limp, refusal to move affected extremities, constitutional symptoms. Older children - limp, fever, point tenderness. On examination, swelling of affected extremity, tenderness, restriction of movements will be present.

Diagnosis:

Suspected based on clinical findings.

Aspirate of affected bone, joint fluid reveal microorganisms.

Histopathology of surgical specimens can also be helpful.

Leucocytosis elevated CRP, ESR, blood cultures.

Plain X-ray

In osteomyelitis -occur in 3 stages

Stage 1: Within 3 days of onset of symptoms -localized, deep soft tissue swelling.

Stage 2: 3-7 days after onset of symptoms. Swelling of muscles with obliteration of interposed translucent fat planes.

Stage 3 :(10 to 21 days) subperiosteal bone resorption, area of bone destruction and periosteal new bone formation.

In septic arthritis - capsular swelling

In myositis - soft tissue swelling, widened fascial plane

MRI:

Imaging modality of choice in osteomyelitis. Accurately delineates the pus collection, extent of involvement. T_1 weighted images show decreased signal due to marrow edema and T_2 weighted images show increased signal intensities.

USG:

It helps in identifying fluid collection in joint, muscle abscess.

Technetium (Tc 99 m) bone scan - reveals increased up take in affected area.

Treatment:

In case of muscle abscess - surgical drainage is necessary. Septic arthritis - arthrotomy, drainage. Osteomyelitis – Surgical exploration, if medical treatment fails. Depending on etiology parenteral antibiotics is chosen. Since Staphylococcus aureus is the commonest organism intravenous Naficillin or Oxacillin (200 mg/kg/day) is the initial choice. When MRSA is suspected – i.v. Clindamycin (40 mg/kg/day) or Vancomycin (60 mg/kg/day) is used. For H.influenzae – i.v. 3rd generation cephalosporin is the initial choice. In case of Pseudomonas or gram negative

enteric organism – ceftazidime and aminoglycoside combination should be used. In case of anaerobic infection clindamycin should be added.

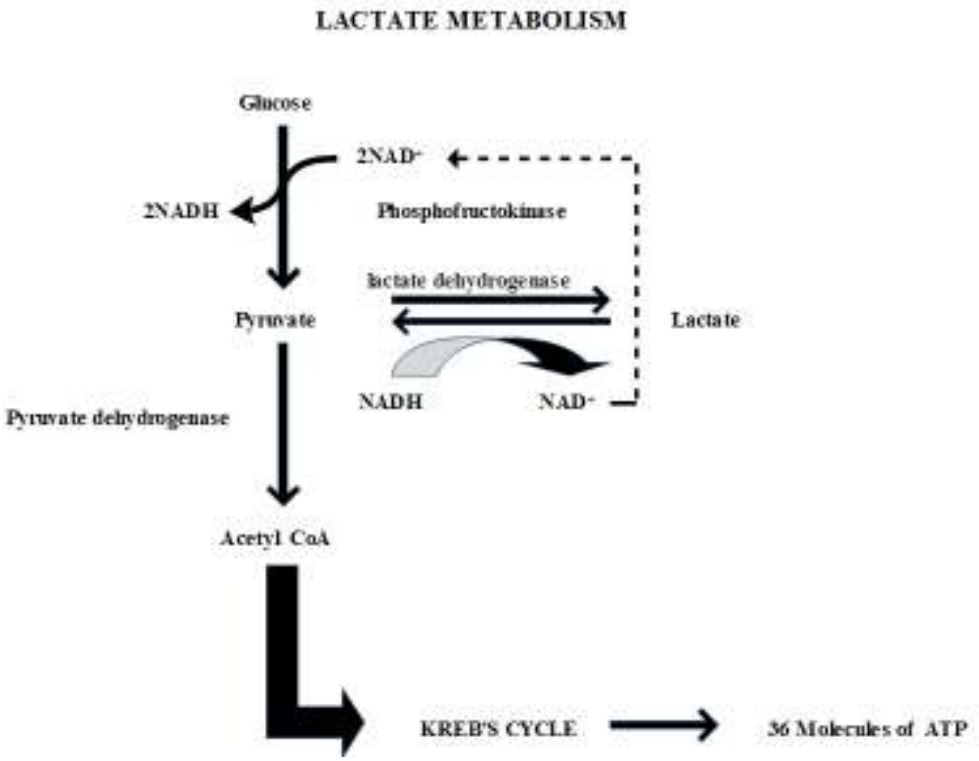
LACTATE

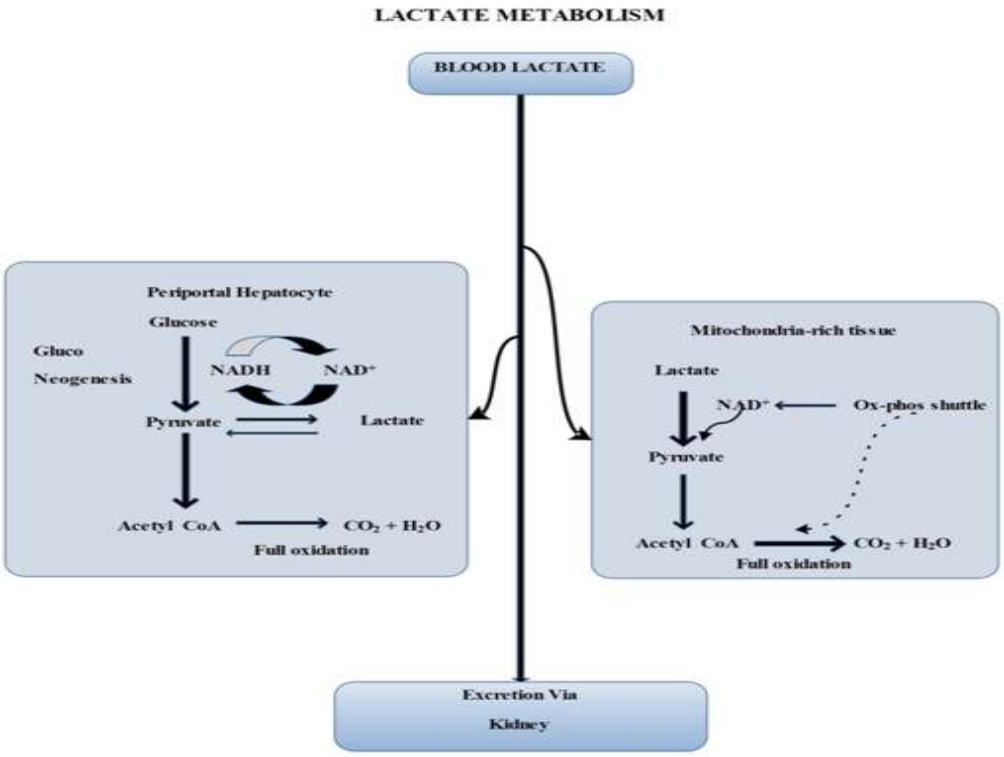
HISTORY

Karl Wilhelm Scheele, a Swedish chemist first described lactate in 1780[17]. He discovered lactate in sour milk. Jon Jacob Benzalieus described the same in the year 1807 in muscle tissue of hunted stage[17]. Trasaburo Araki and Herman Zillessen demonstrated the relationship between tissue hypoxia and lactate production[18]. In humans lactate in blood was first demonstrated in women who died of pueperal fever in 1843 by German physician and chemist, Joseph Schere[19]. In living patients, it was demonstrated by Carl Folworezing in 1858[17].

Initially, hyperlactatemia was considered primarily as a result of anaerobic metabolism due to inadequate tissue oxygen delivery. Only in later half of 20th century, understanding of elevated serum lactate has changed. Importance of hyperlactatemia included disease states other than tissue hypoxia.

FIG 4: LACTATE METABOLISM





LACTATE – METABOLISM

Glucose is metabolised via glycolytic pathway in the body to pyruvate. Pyruvate once generated can enter into any one of the following pathways

(i) Tricarboxylic acid pathway or citric acid cycle in the mitochondria to produce energy in the form of ATP. Under aerobic condition through oxidation 38 molecules of ATP can be produced.

(ii) Can be converted to lactate by enzyme lactate dehydrogenase.

(iii) Can be directed to gluconeogenesis for glucose production.

(iv) Production of alanine by transamination.

Normal lactate production is about 0.8 mmol/kg/hr. All tissue can produce lactate. Under physiologic conditions, source of lactate production include skin (25%), skeletal muscle (25%), brain (20%), erythrocytes (20%) and intestine (10%). Metabolism of lactate occurs mainly in liver. About 60% of lactate produced, enter periportal hepatocytes and get converted to glucose and glycogen via the Cori cycle.

Conversion of pyruvate to lactate occurs under certain circumstances[20]

1. Glycolysis requires NAD^+ which is produced to some extent by pyruvate to lactate conversion. Presence of NADH controls the above rate of conversion. Mainly Malate aspartate shuttle and to certain extent glycerol phosphate shuttle pathway help to keep NADH levels

low. If the rate of glycolysis surpass the ox-phosphate shuttle systems, concentration of NADH rises and thereby lactate production also increase.

2. Increased aerobic glycolysis
    (i) Seen in response to cytokine release, at site of infection, inflammation
    (ii) Systemic hypoperfusion as in shock.
    (iii) Hypoxemia.
    (iv) Increased catecholamines as in Pheochromocytoma
3. Decreased activity of pyruvate dehydrogenase
    (i) Congenital abnormalities of pyruvate dehydrogenase enzymes
    (ii) Deficiency of co-factor – thiamine
4. Decreased clearance
    (i) Impaired liver function
    (ii) Mitochondrial dysfunction
    (iii) Drug like metformin inhibit gluconeogenesis
    (iv) Alcohol intoxication causing impaired gluconeogenesis and also impaired pyruvate dehydrogenase activity

In physiological conditions lactate is not normally excreted by kidneys, because the renal threshold is approximately 5 to 6 mmol/l[20]. Renal cortex produce glucose from lactate by gluconeogenesis. When renal blood flow is compromised as in septic shock, clearance of lactate can be impaired causing elevated lactate levels.

LACTATE AND SEPTIC SHOCK:

Many pathological conditions cause elevation of lactate level by increased production or impaired clearance. In septic shock, increase in lactate occurs due to tissue hypoxemia, hypermetabolism and impaired clearance[21]. These findings make serum lactate - a potential biomarker in children with septic shock.

REVIEW OF LITERATURE

Koliski et al conducted a prospective observational study in 75 children admitted in intensive care unit for various illnesses. Patients were divided into two group based on lactate level. Mortality was higher in patients with lactate ≥ 18 mg/dl (30% versus 12%). Lactate level at 24 hours had best sensitivity 55.6 % and specificity 97.2%. They reported that chance of survival was high if lactate level was reduced within 24hours of admission[22].

Kana ram Jat et al conducted a prospective observational study in 30 children admitted to PICU with septic shock. Their aim was to correlate serum lactate level in children with septic shock with survival. Serum lactate level was measured in arterial blood 0 - 3, 12 and at 24 hours after admission. PRISM –III score and demographic characteristic of all children were recorded. Primary outcome measured was survival or death. Analysis revealed higher lactate levels among non-survivors compared to survivors. Lactate value of more than 45 mg/dl (5 mmol/l) was significantly associated with poor outcome. Lactate levels also correlated with PRISM III score[23].

A prospective cohort study was conducted by **Scott et al** in children younger than 19 years. Their objective was to test the utility of serum lactate testing in pediatric emergency department patients with system

inflammatory response syndrome. Outcome measured was organ dysfunction within 24 hours of triage. Secondary outcomes measured were disposition, serious bacterial infection, treatment and mortality. 239 children were subjects. The hyperlactatemia group (lactate > 4 mmol/l) had a relative risk of 5.5 of developing organ dysfunction at 24 hours. In hyperlactatemia group, the sensitivity was 31% and specificity was 94% for predicting organ dysfunction. They concluded that early hyperlactatemia is significantly associated with increased risk of organ dysfunction, resuscitative therapies, admission to intensive care unit and bacterial infection[24].

Zhoux et al retrospectively studied the relationship between blood lactate level and disease severity in 232 critically ill children. According to blood lactate level within 24 hours of admission, patients were classified into three groups: Normal, high lacticemia and lactic acidosis groups. Pediatric critical illness score and prognosis were compared among the three groups. Prognosis in lactic acidosis group was significantly lower and mortality (28.6%) was significantly higher than in normal group[25].

Duke et al conducted a prospective study among 31 children admitted with sepsis. Their objective was to assess the markers of perfusion which best discriminate survivors from non-survivors. Arterial lactate was measured at admission, 12, 24 and 48 hours. The positive predictive value

for death was 56% for blood lactate level greater than 3 mmol/L measured at 12 hours. The positive predictive value for death was 71% for blood lactate level greater than 3 mmol/l measured at 24 hours. Blood lactate was the earliest predictor of outcome of 56% in children with sepsis[26].

Garcia Sanz et al performed a prospective study in 500 consecutive children admitted to PICU. Their objective was to analyse and compare the prognostic value of blood lactate and pediatric index of mortality (PIM) score on admission to PICU. Predictive ability of PIM score and lactate relating to mortality and duration of stay in the hospital were analysed. Mean probability of death according to PIM score was significantly higher in non-survivors. Lactate concentration in non-survivors was 3.5 mmol/l which was statistically significant when compared to survivors, 1.5 mmol/l ($P < 0.001$).The area under ROC curve was 0.76 [95% CI 0.67 to 0.85] which was also significant $p< 0.04$[27].

Hatherill et al conducted a prospective study to examine relationship between early hyperlactatemia, acidosis and mortality in children admitted to intensive care. 755 critically ill children were screened. 50 children with hyperlactatemia were studied. PRISM score, length of stay in PICU and outcome were analysed. Mortality in study group was 64 %. In non-survivors, median peak lactate level was 6.8 mmol/l, which was

significantly higher compared to survivors 5 mmol/l. Average lactate level was 2.4 mmol /L in survivors, compared to 4.5 mmol/l in non survivors (P = 0.0003). They concluded that persistent hyperlactatemia even after 24 hours of admission is associated with higher mortality in critically ill children[28].

Prospective study was conducted by **Barat Ramakrishna et al** to determine whether blood lactate measured at time of presentation to hospital predicted outcome in children with pneumonia. The relative risk of death if lactate level above 2 mmol/l was 7.48, sensitivity was 92%, specificity was 39%, Multivariate analysis showed that hypoxemia, hyperlactatemia, age ≤ 12 months were independent risk factors for death from pneumonia[29].

Mark E.Mikkelson et al performed a retrospective cohort study in adult patients presenting to the emergency department with severe sepsis. 830 patients was included. Primary objective of the study was to find whether the association between initial serum lactate and mortality is significantly related to clinically apparent organ dysfunction and shock. The primary outcome measured was 28 day mortality. 60 days mortality was considered as secondary outcome. Initial venous lactate was categorised as low (< 2 mmol/l), intermediate (2 - 3.9 mmol/l) or high (≥ 4 mmol/l). They

reported that intermediate and high serum lactate levels are independently associated with mortality[30].

In a study performed by **Hussain et al**, lactate level was measured at admission and at 24 hours. 137 surgical intensive care unit patients were studied. Initial and 24 hours lactate level was significantly elevated in non survivors versus survivors ($p = 0.002$). Mortality also increased with increasing time for normalization of lactate. Mortality rate was 10% if lactate normalized within 24 hours, 24% for > 48 hours and 67% if lactate did not return to normal[31].

Marecaux et al conducted a prospective observation study on 38 adult patients with septic shock. Serum levels of tumour necrosis factor – alpha, interleukin - 6 and blood lactate were measured serially at admission, 24 and 48 hours. Admission blood lactate levels were higher in non survivors than survivors and decreased significantly in survivors than non-survivors. They also reported that blood lactate was a better prognostic indicator than TNF - α and

IL – 6[32].

Phua J et al compared the prognostic utility of lactate procalcitonin, amino terminal pro – B – type natriuretic peptide with each other and with cytokines like interleukin – 1 β, interleukin – 6 and TNF α levels and clinical

severity scores and their prognostic utility in septic shock. 72 adult patients with septic shock were studied. The biomarkers were measured on first 3 days of stay in intensive care unit. Rising trend in lactate and procalcitonin level between day 2 and 3 were better prognostic indicators. They concluded that serial lactate level will be useful for prognostication in septic shock[33].

A Prospective cohort study in 32 adult patients with septic shock was studied by **Bernardin G et al** to identify early prognostic markers of septic shock. Mean arterial blood pressure and lactate were measured at admission and at 24 hours. Among 32 patients, 18 survived. After 24 hours, non – survivors had significantly lower mean arterial blood pressure and higher lactate level ($p < 0.01$) than survivor. 24 hours changes of lactate and blood pressure were also of prognostic value. Lactate level equal to or greater than 3.5 mmol/ l was independently associated with poor survival[34].

Murat Basaran et al conducted a prospective observational study in 60 infants operated for congenital heart diseases. Serum lactate was measured at 3 hours, 6 hours and 12 hours post operatively. Blood lactate level of 4.8 mmol/l was taken as threshold. Mortality was significantly higher in children with lactate > 4.8 mmol/l[35].

A prospective observation study comparing prognostic value of blood lactate, gastric intramucosl pH in patients with severe sepsis was conducted

by **Friedman .G et al**. 35 consecutive patients with severe sepsis were included in the study. There was no significant difference in blood lactate concentration between survivor and non-survivors [3.2 ± 1.5 Vs 2.8 ± 2.3 meq/l]. But 4 hours and 24 hours lactate remained high in survivors and progressively decreased in survivors. Both lactate and intramucosal pH were reliable prognostic indicators in severe sepsis[36].

A prospective cohort study was carried out in emergency department by **Hisamuddin et al**. 51 adult patients with sepsis induced hypotension and septic shock was included. Outcome measured was 30 day mortality. Twenty two deaths occurred within 30 days follow up. Overall mean lactate was 3.52 mmol/l. Analysis revealed an increase in lactate level in emergency department was associated with an increased risk of death. For every increment of lactate value of 1 mmol/l hazards of dying are expected to increase by 1.5 times ($p < 0.001$)[37].

Ole kruse et al performed a systematic analysis of about 66 articles using Pub med, Cochrane, Central Register of Controlled trial, Cochrane database of systemic review. Finally 33 articles were selected for analysis. Their aim was to examine whether blood lactate levels are predictive of hospital mortality in acute care settings which included, patients assessed pre-hospital, in trauma center and Intensive Care Unit. The review

concluded that blood lactate is useful for risk assessment in acutely ill patients. Serial lactate is useful in predicting in hospital mortality. Lactate level greater than 2.5 mmol/l should be closely monitored for signs of deterioration[38].

JUSTIFICATION OF THE STUDY

Sepsis and septic shock is one of the leading causes for admission in intensive care unit. Septic shock causes millions of children deaths every year. Mortality is high even with advanced intensive care. Studies have been conducted and new researches are ongoing to find biomarkers which will help in early identification, prognostication and treatment in critically ill children. This will help to reduce morbidity and mortality. Studies in adults have demonstrated that serum is a useful predictor of outcome in septic shock. Studies in children are limited. This study aimed to correlate serum levels of lactate with the poor outcome and its usefulness in predicting the mortality in children with septic shock.

OBJECTIVES OF THE STUDY

1. To determine the association between serum lactate level and mortality in pediatric septic shock.
2. To determine whether serial determination of serum lactate level is a predictor of outcome in pediatric septic shock.
3. To determine the association between organ dysfunction, presence of anemia, malnutrition, diagnosis and outcome in pediatric septic shock.

SUBJECTS AND METHODS

STUDY DESIGN:

Nested case control study

STUDY PLACE:

Pediatric Intensive Care Unit, Coimbatore Medical College and Hospital

STUDY PERIOD:

December 2011 – September 2012

STUDY POPULATION:

3 months – 12 years children admitted in PICU with septic shock

INCLUSION CRITERIA

All Children from age of 3 months to 12 years admitted with septic shock in PICU during the study period between 7am and 7 pm.

EXCLUSION CRITERIA

1. Children who received pre-hospital treatment in the form of fluid boluses.
2. Inborn errors of metabolism.

SAMPLE SIZE:

Sample size was estimated using the formula, $Y= (\mu 1-\mu 2)/\sigma$

Y-difference between two population means

σ -population standard deviation

Based on Previous studies,

$\mu 1 = 5.49$, $\mu 2 = 5.21$, SD or $\sigma = 0.56$ and Y=0.5

Corresponding to power at 0.50, estimated sample size was 49.

SAMPLING TECHNIQUE:

Children admitted with septic shock on consecutive days between 7 am and 7 pm during the study period.

DEFINITIONS:

SIRS (Systemic Inflammatory Response Syndrome)[39]

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

1) Core temperature of > 38.5°C or < 36°C.
2) Tachycardia, defined as a mean heart rate > 2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5 to 4 hr time period.

Or

For children < 1 year old: bradycardia, defined as a mean heart rate < 10th percentile for age in the absence of external vagal stimulus, beta-blocker

drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5 hr time period.

3) Mean respiratory rate greater than two standard deviation above normal for age or need for mechanical ventilation.
4) Increased or reduced white blood cell count for age (not secondary to chemotherapy-induced leukopenia) or > 10% immature neutrophils.

Infection

A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, and chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans).

Sepsis

SIRS in the presence of or as a result of suspected or proven infection.

Severe sepsis

Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome or two or more other organ dysfunctions.

Septic shock

Sepsis and cardiovascular organ dysfunction.

Cardiovascular dysfunction

Despite administration of isotonic intravenous fluid bolus of greater than 40 ml/kg in 1 hour.

Decrease in BP (hypotension) < 5th percentile for age or

Systolic BP > 2 SD below normal for age (*a)* OR

Need for vasoactive drug to maintain BP in normal range

(Dopamine> 5 mcg/kg/min or dobutamine, epinephrine, or

Norepinephrine at any dose) OR Two of the following

Unexplained metabolic acidosis: base deficit > 5.0 meq/l

Increased arterial lactate > 2 times upper limit of normal

Oliguria: urine output < 0.5 ml/kg/hr

Prolonged capillary refill: > 5 secs

Core to peripheral temperature gap > 3°C

Dysfunction of Respiratory System (b)

PaO_2/FIO_2< 300 in absence of cyanotic heart disease or

Pre-existing lung disease OR

$PaCO_2$> 65 torr or 20 mm Hg over baseline $PaCO_2$ OR

Proven need (*c)* or > 50% FIO_2 to maintain saturation > 92% OR

Need for non elective invasive or non-invasive mechanical ventilation (*d)*.

Neurologic dysfunction

Glasgow coma score < 11 OR

Acute change in mental status with a decrease in Glasgow

Coma score > 3 points from abnormal baseline

Dysfunction of haematological system

Platelet count < 80,000/mm^3 or a drop in platelet count of 50% from highest value recorded over the past 3 days (for chronic haematology /oncology patients) OR

International normalized ratio > 2

Renal dysfunction

Serum creatinine > 2 times upper limit of normal for age or 2 fold increase in baseline creatinine

Hepatic dysfunction

Total bilirubin > 4 mg/dL (not applicable for new-born) OR

Serum alanine transaminase 2 times upper limit of normal for age

MODS (Multi Organ Dysfunction)

Presence of two or more organ dysfunction.

(*a)* See Table (I);

Table (I)

Age - Specific vital signs and laboratory values*

Age group	Heart rate		Respiratory rate Breaths/min	Leukocyte count x1000/cu.mm	SBP
	Tachycardia	Bradycardia			
0-1	>180	<100	>50	> 34	<65
1 Week to 1 month	>180	<100	>40	>19.5 or <5	<75
1 month to 1 year	>180	<90	>34	>17.5 or <5	<100
2 - 5 years	>140	NA	>22	>15.5 or <6	<94
6 - 12 years	>130	NA	>18	>13.5 or <4.5	<105
13 - 18 years	>110	NA	>14	>11or <4.5	<117

*Lower values for heart rate, leukocyte count, systolic blood pressure (SBP) are for the 5th percentile and upper values for heart rate, respiratory rate, or leukocycte count for the 95th percentile. NA – Not Applicable

(*b)* Acute respiratory distress syndrome must include acute onset, new onset of bilateral infiltrates on CXR, PaO2/ FIO_2 ratio < 200 mm Hg, and no

evidence of left heart failure. Acute lung injury is defined similarly except thePaO_2/FIO_2 ratio must be < 300 mm Hg;

(*c)* Proven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required;

(*d)* In postoperative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated.

WHO criteria for Anemia:

6 months to 5 years - < 11g/dl

5 to 12 years - < 11.5g/dl

Under nutrition:

Determined by WHO criteria[40]. Z - score cut off point < -2 standard deviation is under nutrition.

Serum sodium: 135 to 145 meq/l; Serum potassium: 3.5 to 5.5meq/l

Arterial lactate: 4.5 to 14.4 mg/dl (0.5-1.6 mmol/l)[41]

MANEUVER:

Children between 3 months to 12 years admitted with clinical diagnosis of septic shock were included. Clinical diagnosis of septic shock was made based on pediatric assessment triangle – temperature instability with warm or cold shock or hypotensive shock[42].

Following clinical data were recorded in proforma after obtaining consent from the parents–age, sex, clinical history, examination findings, duration of stay, Treatment after admission in PICU, vital parameters, complete blood count, peripheral smear, blood culture, urine analysis, urine culture, blood urea, serum electrolytes, serum creatinine, serum bilirubin, serum alanine transaminase, Blood gas analysis was obtained in all cases. Prothrombin time, activated partial thromboplastin time was measured if clinically indicated. CSF analysis was done in children with clinical suspicion of CNS infection.

Lactate in arterial blood was measured at 0 to 3 hours and after 24 hours of admission. Lactate level was estimated using enzymatic method at the Lister laboratories, Coimbatore. Cobos E400 colorimeter was used for measurement. The principle is lactate oxidase catalyses the oxidation of lactate to pyruvate and hydrogen peroxide. Peroxidase then catalyses the reaction of hydrogen peroxide with a hydrogen donor, in the presence of 4 aminophenazone to form a dye. Color intensity, measured at 550 nm, is proportional to lactate concentration in the sample.

RESULTS

STATISTICAL ANALYSIS:

Data were analyzed using SPSS software version 17 and MedCalc software version 15. Data were interpreted using descriptive and inferential statistics. The Chi-square test was used to test the statistical significance of relationship between two variables. Student **T** test was used to determine if there is a significant difference between the mean of two groups. The cut off value was estimated by using Receiver Operating Characteristics Curve (ROC) analysis[43]. Area under the ROC curve more than 0.5 indicates that the test predicts outcome better than no chance. Optimum cut off values were determined using associated criterion. The curve represents graphical relationship between sensitivity and 1 -specificity. Odds ratio is calculated from measure of association between exposure and outcome.

Screening test results	Outcome		Total
	Poor	Good	
Positive	a (True positive)	b (False positive)	a + b
Negative	a (False positive)	d (True negative)	c + d

PPV- Positive Predictive value = [a / (a + b)] x 100

NPV- Negative Predictive value = [d / (c + d)] x 100

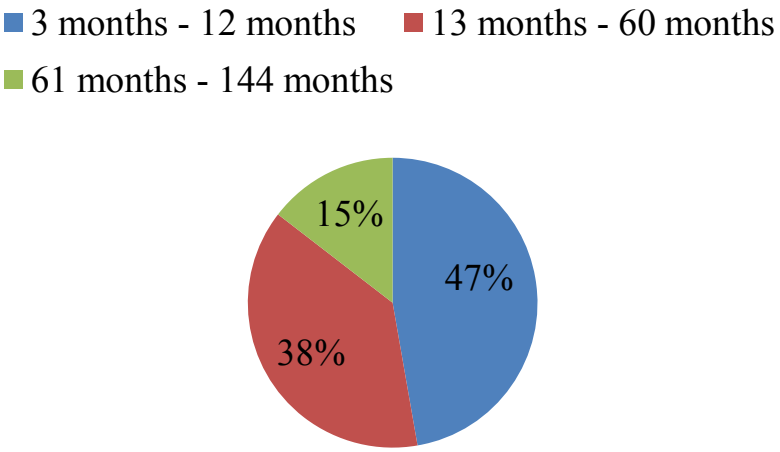
AGE DISTRIBUTION OF STUDY POPULATION

TABLE 1

Age	Frequency	Percent
3 months - 12 months	26	47.3%
13 months - 60 months	21	38.2%
61 months - 144 months	8	14.5%
Total	55	100%

CHART 1

AGE



Out of 55 children studied, 26 (47.3%) children were between 3 month and 1 year. 21 children (38.2%) were between 1 and 5 years. 8 children (14.5%) were between 5 and 12 years

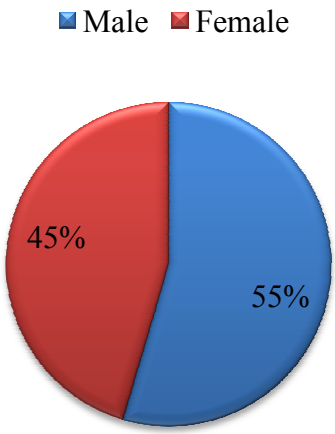
GENDER

TABLE 2

Sex	Frequency	Percent
Male	30	54.5%
Female	25	45.5%
Total	55	100%

CHART 2

GENDER



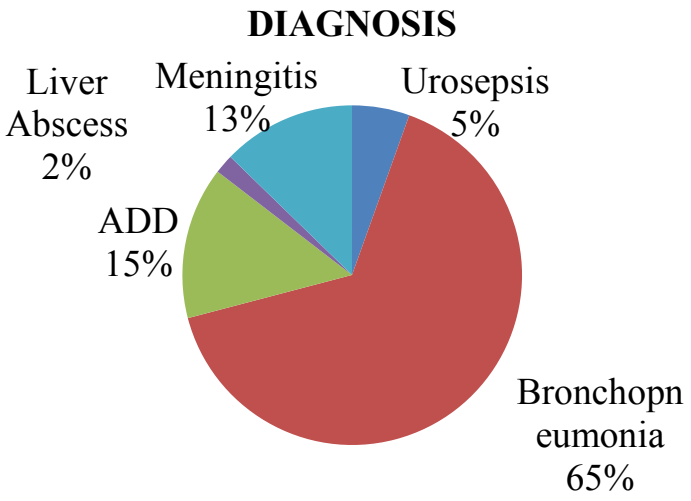
Among the study population, 30 were male children and 25 were female children.

DIAGONSIS

TABLE 3

Diagnosis	Frequency	Percent
Urosepsis	3	5.5%
Bronchopneumonia	36	65.5%
Acute Diarrhoeal Disease	8	14.5%
Liver Abscess	1	1.8%
Meningitis	7	12.7%
Total	55	100%

CHART 3



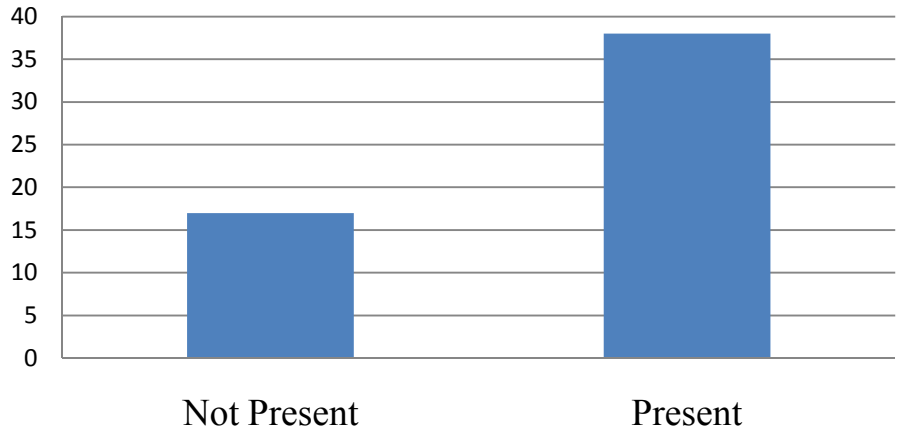
ANEMIA

TABLE 4

Anemia	Frequency	Percent
Not Present	17	30.9%
Present	38	69.1%
Total	55	100%

CHART 4

ANEMIA



Among 55 children admitted in the PICU in the study period, anemia was observed 38 (69.1%) cases.

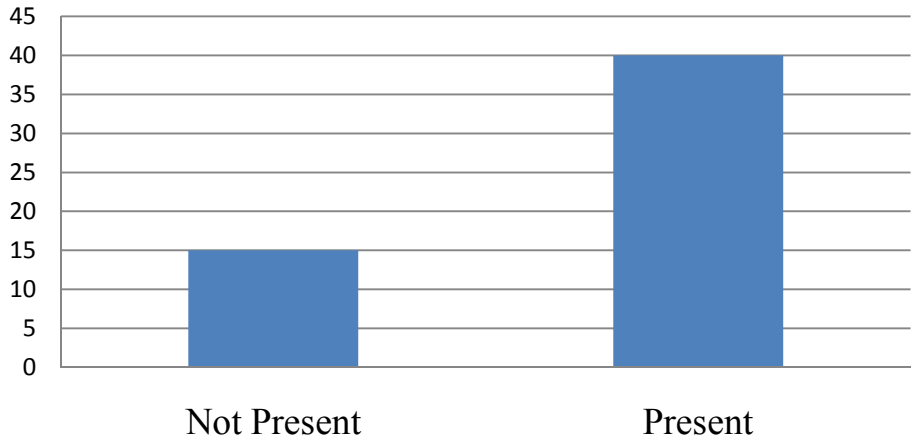
UNDER NUTRITION

TABLE 5

Under nutrition	Frequency	Percent
Not Present	15	27.3%
Present	40	72.7%
Total	55	100%

CHART 5

UNDER NUTRITION



Among the study population, under nutrition was present in 40 (72.7%) cases.

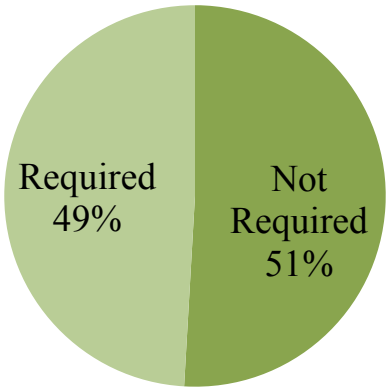
VENTILATION REQUIREMENT:

TABLE 6

Ventilation	Frequency	Percent
Not Required	28	50.9%
Required	27	49.1%
Total	55	100%

CHART 6

VENTILATION



Among the study population, ventilation was required in 27 (49.1%) cases.

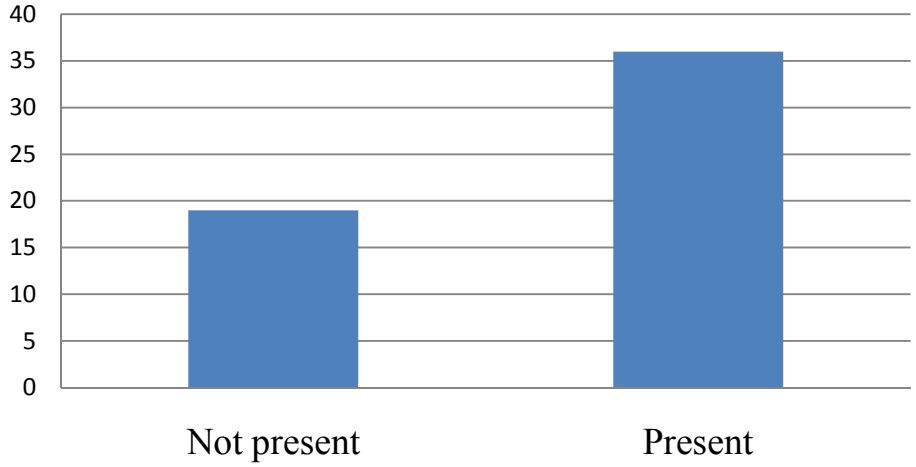
ORGAN DYSFUNCTION

TABLE 7

Organ dysfunction	Frequency	Percent
Not present	19	34.5%
Present	36	65.5%
Total	55	100%

CHART 7

ORGAN DYSFUNCTION



In the study population, organ dysfunction was observed in 36 (65.5%) cases.

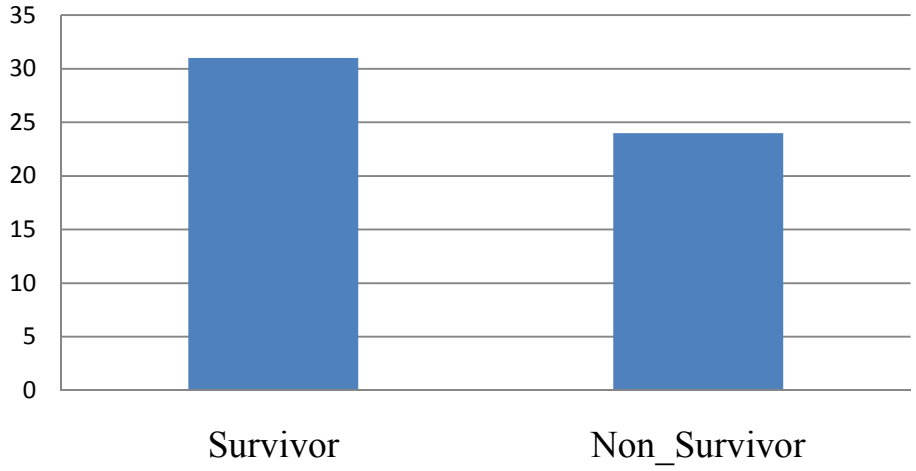
OUTCOME:

TABLE 8

Outcome	Frequency	Percent
Survivors	31	56.4%
Non Survivors	24	43.6%
Total	55	100%

CHART 8

OUTCOME



Among the study population, survivors were 31 (56.4%) cases and non survivors were 24(43.6%) cases.

LACTATE AT (0 TO 3) HOURS VS OUTCOME

TABLE 9

LACTATE AT 0-3 hrs	OUTCOME	
	Survivors	Non-Survivors
20.1 – 30.0	19(95.0 %)	1(5 .0%)
30.1 – 40.0	7(100.0 %)	-
40.1 – 50.0	3(33.3 %)	6(66.7 %)
50.1 – 60.0	1(20.0 %)	4(80.0 %)
60.1 – 70.0	1(10.0 %)	9(90.0%)
70.1 – 80.0	-	4(100.0 %)

The Chi square value is 36.2; p value < 0.001. There is a significant association between lactate level (0 – 3 hours) and outcome. From the table it can be inferred that with increase in lactate level, the number of non survivors increase. Above the cut off value of ≥ 41mg/dl (from ROC analysis) number of non survivors are 23. Lactate level greater than 70 mg/dl, had 100% mortality.

LACTATE AT 24 HOURS VS OUTCOME

TABLE 10

LACTATE AFTER 24 hrs	OUTCOME	
	Survivors	**Non-Survivors**
10.1 – 20.0	13(92.9 %)	1(7.1 %)
20.1 – 30.0	14(100.0 %)	-
30.1 – 40.0	1(33.3 %)	2(66.7 %)
40.1 – 50.0	2(25.0 %)	6(75.0%)
50.1 – 60.0	-	7(100.0%)
60.1 – 70.0	1(12.5%)	7(87.5%)
70.1 – 80.0	-	1(100 %)

The Chi Square value is 40.2; p value is < 0.001. There is a significant association between lactate level 24hours and outcome. From the table it can be inferred that with increase in lactate level, the number of non survivors increase. Above the cut off value of ≥ 39.2 mg/dl (from ROC analysis) number of non survivors are 21.

LACTATE AT 0 TO 3 HOURS VS OUTCOME

TABLE 11

	Outcome	N	Mean	Std. Deviation
Lactate at 0 to 3hrs	Survivor	31	32.316	10.7871
	Non Survivor	24	58.471	11.4228

Independent Samples Test

		F_0	T	Df	Sig
Lactate at 0 to 3hrs	Equal variances assumed Equal variance not assumed	.483	8.69	53	.000

T value for mean difference in initial lactate level between survivors and non survivors is significant ($p<0.001$).the mean lactate level among survivors and non survivors was 32.3mg/dl and 58.4mg /dl respectively. It can be inferred that initial lactate level is significantly high in non survivors compared with survivors

LACTATE AT 24 HOURS VS OUTCOME

TABLE 12

	Outcome	N	Mean	Std. Deviation
Lactate at 24 hrs after admission	Survivor	31	24.729	10.3953
	Non Survivor	24	53.283	12.2881

Independent Samples Test

		F_0	T	df	Sig
Lactate at 24 hrs after admission	Equal variances assumed	1.73	9.33	53	.000
	Equal variance not assumed				

The T value (9.33) for mean difference in lactate level measured at 24 hours between survivors and non survivors is significant ($p<0.001$).the mean lactate level among survivors and non survivors was 24.7mg/dl and 53.2 mg /dl respectively. It can be inferred that lactate level at 24 hours is significantly high in non survivors compared with survivors.

AGE VS OUTCOME

TABLE 13

AGE	OUTCOME			
	SURVIVORS	%	NON SURVIVORS	%
3 months – 12 months	16	61.5	10	38.5
13 months – 60 months	10	47.6	11	52.4
61 months – 144 months	5	62.5	3	37.5

Non survivors were high (52.4%) in age group 13 to 60 months. The Chi square value is 1.058 for the association between age and outcome which is not statistically significant (p=0.58). It can be inferred that there is no association between age and outcome.

ANEMIA VS OUTCOME

TABLE 14

ANEMIA	OUTCOME			
	SURVIVORS	%	NON SURVIVORS	%
Present	22	57.9	16	42.1
Not Present	9	52.9	8	47.1

Among children with anemia, survivors were 22 (57.9%) and non survivors were 16 (42.15). The Chi square value 0.117 for the association between anemia and outcome are not statistically significant (p = 0.732). It

can be inferred that there is no association between presence of anemia and outcome.

DIAGNOSIS VS OUTCOME

TABLE 15

DIAGNOSIS	OUTCOME			
	SURVIVORS	%	NON SURVIVORS	%
Urosepsis	3	100.0	-	-
Bronchopneumonia	18	50.0	18	50.0
Acute diarrhoeal disease	6	75.0	2	25.0
Liver Abscess	1	100.0	-	-
Meningitis	3	42.9	4	57.1

Among children with bronchopneumonia mortality was 50%. In children with meningitis mortality was 57.1%. The Chi square value 5.338 for the association between diagnosis and outcome is not statistically significant (p=0.254). It can be inferred that there is no association between diagnosis and outcome.

UNDER NUTRITION VS OUTCOME

TABLE 16

UNDER NURTRITION	OUTCOME			
	SURVIVORS	%	NON SURVIVORS	%
Present	19	47.5	21	52.5
Not Present	12	80.0	3	20.0

52.5% children with under nutrition expired. The Chi square value 4.685 for the association between undernutrition and outcome is statistically significant (p=0.030). It can be inferred that there is association between presence of undernutrition and outcome.

REQUIRED VENTILATION VS OUTCOME

TABLE 17

VENTILATION	OUTCOME			
	SURVIVORS	%	NON SURVIVORS	%
Required	9	33.3	18	66.7
Not Required	18	78.6	6	21.4

Need for ventilation was present in 18 non survivors. The Chi square value 11.43 for the association between requirement of ventilation and

outcome is statistically significant (p=0.001). It can be inferred that there is association between requirement of ventilation and outcome.

ORGAN DYSFUNCTION VS OUTCOME

TABLE 18

ORGAN DYSFUNCTION	OUTCOME			
	SURVIVOR	%	NON SURVIVOR	%
Present	14	38.9	22	61.1
Not Present	17	89.5	2	10.5

Oxygen dysfunction, was present in 61.1% of non survivors. The Chi square value 12.939 for the association between presence of organ dysfunction and outcome is significant (p=0.001). It can be inferred that there is association between presence of organ dysfunction and outcome.

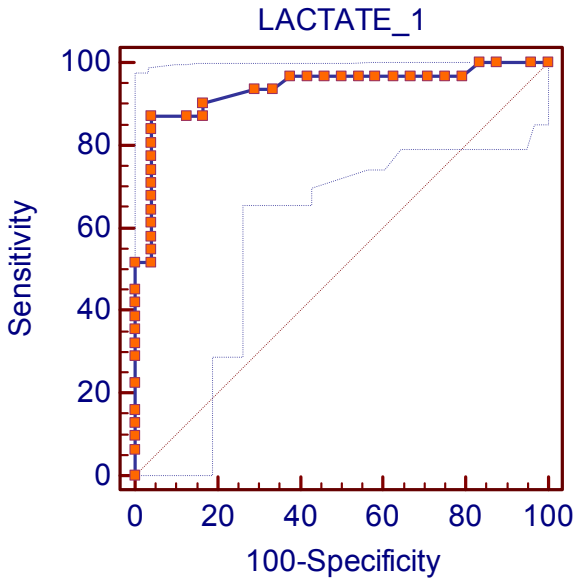
RECEIVER OPERATING CHARACTERISTICS CURVE ANALYSIS

TABLE 19

Variable	Lactate at 0 to 3 hrs	
Sample size		55
Positive group	OUTCOME =1	31
Negative group	OUTCOME = 0	24

Area under the ROC Curve

Area under the ROC curve (AUC)	0.935
Standard Error	0.0347
95 % Confidence interval	0.834 to 0.984
Z statistic	12.519
Significance level P(Area =0.5)	< 0.0001
Associated Criterion	≥ 41



Criterion values and coordinates of the ROC curve

Criterion	Sensitivity	95 % CI	Specificity	Criterion	Sensitivity	95 % CI	Specificity
≥21	0	0.0 - 11.2	100	≥43.4	87.1	70.2 - 96.4	87.5
≥21	6.45	0.8 - 21.4	100	≥45.7	87.1	70.2 - 96.4	83.33
≥22.8	9.68	2.0 - 25.8	100	≥48.4	90.32	74.2 - 98.0	83.33
≥23	12.9	3.6 - 29.8	100	≥49.8	93.55	78.6 - 99.2	70.83
≥24.8	16.13	5.5 - 33.7	100	≥51	93.55	78.6 - 99.2	66.67
≥25.6	22.58	9.6 - 41.1	100	≥55.6	96.77	83.3 - 99.9	62.5
≥25.8	29.03	14.2 - 48.0	100	≥57.8	96.77	83.3 - 99.9	58.33
≥26.2	32.26	16.7 - 51.4	100	≥58.8	96.77	83.3 - 99.9	54.17
≥26.4	35.48	19.2 - 54.6	100	≥60.2	96.77	83.3 - 99.9	50
≥26.8	38.71	21.8 - 57.8	100	≥60.9	96.77	83.3 - 99.9	45.83
≥27.4	41.94	24.5 - 60.9	100	≥62.4	96.77	83.3 - 99.9	41.67
≥28.2	45.16	27.3 - 64.0	100	≥63.2	96.77	83.3 - 99.9	37.5
≥28.6	51.61	33.1 - 69.8	100	≥64.2	96.77	83.3 - 99.9	33.33
≥28.7	51.61	33.1 - 69.8	95.83	≥64.6	96.77	83.3 - 99.9	29.17
≥28.8	54.84	36.0 - 72.7	95.83	≥66.2	96.77	83.3 - 99.9	25
≥29	58.06	39.1 - 75.5	95.83	≥68	96.77	83.3 - 99.9	20.83
≥29.8	61.29	42.2 - 78.2	95.83	≥68.8	100	88.8 - 100.0	16.67
≥31	64.52	45.4 - 80.8	95.83	≥70.2	100	88.8 - 100.0	12.5
≥31.2	67.74	48.6 - 83.3	95.83	≥72.4	100	88.8 - 100.0	4.17
≥32.4	70.97	52.0 - 85.8	95.83	≥76	100	88.8 - 100.0	0
≥33.8	74.19	55.4 - 88.1	95.83				
≥37.2	77.42	58.9 - 90.4	95.83				
≥38	80.65	62.5 - 92.5	95.83				
≥39.4	83.87	66.3 - 94.5	95.83				
≥41	**87.1**	**70.2 - 96.4**	**95.83**				

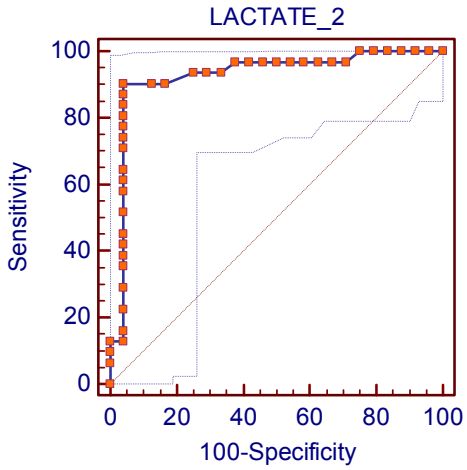
The area under ROC curve for lactate measured at 0 to 3 hours is 0.935 which is statistically significant. The optimum cut off value for lactate at 0 to 3 hours as observed from receiver operating characteristics curve is ≥ 41 mg /dl (4.55 mmol/ L). The sensitivity was 87.1% and specificity was 95.8%

TABLE 20

Variable	LACTATE at 24 Hours	
Sample size		55
Positive group	OUTCOME =1	31
Negative group	OUTCOME = 0	24

Area under the ROC Curve

Area under the ROC curve (AUC)	0.926
Standard Error	0.0431
95 % Confidence interval	0.823 to 0.979
Z statistic	9.874
Significance level P(Area =0.5)	<0.0001
Associated criterion	≥39.2



Criterion values and coordinates of the ROC curve

Criterion	Sensitivity	95 % CI	Specificity	Criterion	Sensitivity	95 % CI	Specificity
≥16	0	0.0 - 11.2	100	≥39.6	90.32	74.2 - 98.0	87.5
≥16	6.45	0.8 - 21.4	100	≥40.6	90.32	74.2 - 98.0	83.33
≥16.4	9.68	2.0 - 25.8	100	≥45.2	93.55	78.6 - 99.2	75
≥16.6	12.9	3.6 - 29.8	100	≥45.6	93.55	78.6 - 99.2	70.83
≥17.4	12.9	3.6 - 29.8	95.83	≥46.6	93.55	78.6 - 99.2	66.67
≥18.2	16.13	5.5 - 33.7	95.83	≥49.8	96.77	83.3 - 99.9	62.5
≥18.6	22.58	9.6 - 41.1	95.83	≥51	96.77	83.3 - 99.9	58.33
≥18.8	29.03	14.2 - 48.0	95.83	≥51.4	96.77	83.3 - 99.9	54.17
≥19.2	35.48	19.2 - 54.6	95.83	≥52.8	96.77	83.3 - 99.9	50
≥19.8	38.71	21.8 - 57.8	95.83	≥54.6	96.77	83.3 - 99.9	45.83
≥20	41.94	24.5 - 60.9	95.83	≥58.4	96.77	83.3 - 99.9	41.67
≥20.6	45.16	27.3 - 64.0	95.83	≥58.8	96.77	83.3 - 99.9	37.5
≥21	51.61	33.1 - 69.8	95.83	≥59.4	96.77	83.3 - 99.9	33.33
≥22	58.06	39.1 - 75.5	95.83	≥60.2	96.77	83.3 - 99.9	29.17
≥23	61.29	42.2 - 78.2	95.83	≥61	100	88.8 - 100.0	25
≥23.4	64.52	45.4 - 80.8	95.83	≥61.2	100	88.8 - 100.0	20.83
≥24.6	70.97	52.0 - 85.8	95.83	≥64.4	100	88.8 - 100.0	16.67
≥25.2	74.19	55.4 - 88.1	95.83	≥66	100	88.8 - 100.0	12.5
≥26.2	77.42	58.9 - 90.4	95.83	≥68.8	100	88.8 - 100.0	8.33
≥26.8	80.65	62.5 - 92.5	95.83	≥69.4	100	88.8 - 100.0	4.17
≥27.2	83.87	66.3 - 94.5	95.83	≥71.8	100	88.8 - 100.0	0
≥39.2	**90.32**	**74.2 - 98.0**	**95.83**				

The area under ROC curve for lactate measured at 24 hours is 0.926 which is statistically significant. The optimum cut off value for lactate at 24 hours as observed from receiver operating characteristics curve is ≥ 39.2 mg /dl (4.35 mmol/l). The sensitivity was 90.3% and specificity was 95.8%.

TABLE 21

Lactate	Cut-off value	Odds ratio	PPV	NPV	P-Value
0 to 3 hours	≥ 41 mg/dl	119.6	82.1 %	96.2 %	<0.0001
24 hours after	≥ 39.2 mg /dl	65.33	85.1 %	96.4 %	<0.0001

The odds ratio, positive predictive value and negative predictive value for the cut off value of lactate ≥ 41 mg/dl measured at 0 to 3 hours are 119.6, 82.1% and 96.2% respectively. These were statistically significant.

The odds ratio, positive predictive value for the cut off value of lactate ≥ 39.2 mg/dl measured at 24 hours are 65.33, 85.1% and 96.4% respectively. These were statistically significant.

DISCUSSION

The total number of children with septic shock admitted during the study period were 55 in number. Among them 30 were boys and 25 were girls. Anemia was observed in 38 cases. Undernutrition was observed in 40 cases. There were 31 survivors and 24 non survivors. Mortality was 43.6%.

Bronchopneumonia (65.5%) was the most cause of septic shock in our study followed by acute diarrhoeal disease (14.5%), meningitis (12.7%), urosepsis (5.5%). This is comparable to study by **Kolski et al** in which bronchopneumonia was the common infection. This is also comparable to study by **Kana Ram Jat et al** in which bronchopneumonia accounted for 73.3% cases. Mortality in our study was 43.6%. This is comparable to observations by **Kana Ram Jat et al.** Mortality was 50% in their study. In children with urosepsis, E coli was the causative organism.

Organ dysfunction other than cardiovascular dysfunction was observed in 36(65.5%) cases. This is comparable to study by **Kana Ram Jat et al** in which organ dysfunction was observed in 66.7% of cases. Respiratory dysfunction (50%) was the most common next to cardiovascular organ system dysfunction.

From ROC analysis, the optimal cut off value for lactate measured at 0 to 3 hours was $\geq$ 41 mg/dl (4.55 mmol/l). For lactate measured at 24 hours,

the optimal cut off value was ≥ 39.2 mg/dl (4.35 mmol/l). Both initial and lactate at 24 hours were significantly high in non survivors ($p<0.001$). The association between lactate measured at 0 to 3 hours and outcome was significant. Also there was significant association between lactate measured at 24 hours and outcome. Initial lactate level of >41 mg/dl had sensitivity of 87% and specificity of 95.8%. Lactate level at 24 hours had sensitivity of 90% and specificity of 95.8%. High lactate level, presence of organ dysfunction and under nutrition were independently associated with poor outcome.

In our study , initial lactate level of ≥ 41mg/dl (4.55 mmol/l) and 24 hours lactate level of ≥ 39.2 mg/dl (4.35 mmol / l) was significantly associated with poor outcome .This is comparable to previous study conducted by **Kana Ram Jat et al**[23] in which lactate ≥ 5 mmol/l or 45 mg/dl was significantly associated with poor outcome .In contrast to our study, **Duke et al**[26] reported lactate level of ≥ 3 mmol/l was a significant predictor of outcome. But in the study conducted by **Duke et al**[26], children with sepsis were the study population. Barat Ramakrishna et al studied children with pneumonia and reported a cut off > 2mmol/l.

Age, sex and presence of anemia were not significantly different between non survivors and survivors. Presence of undernutrition and organ dysfunction were significantly associated with death.

SUMMARY

- Out of 55 children included in the study, boy children were 30, girl children were 25. 47.3 % of children were under age of 1 year, 38.2 % were between 1 and 5 years, 14.5 % of children were between 5 and 12 years
- Pneumonia (65.5 %) was the most common cause for septic shock
- Anemia was observed in 69.1 % of cases and undernutrition was observed in72.7% of cases
- Organ dysfunction other than cardiovascular dysfunction was observed in 36 (65.5%) children of which respiratory dysfunction was observed in 18 cases
- Mortality in our study was 43.6% out of 55 children with septic shock, 31 children were survivors and 24 children were non survivors.
- Non survivors were high in 13 – 60 months age group.
- Lactate measured at 0 to 3 hours and at 24 hours was significantly high in non survivors
- Apart from serum lactate, presence of organ dysfunction and under nutrition were significantly associated with poor outcome.
- Initial serum lactate value $\geq$ 41 mg/dl (4.55 mmol /L) and serum lactate value of $\geq$ 39.2 mg /dl (4.35 mmol /l) at 24 hours were significant predictors of poor outcome in children with septic shock.

CONCLUSION

Septic shock is a common cause for mortality and morbidity in children. Early recognition and goal directed therapy is necessary to prevent complications.

Our study demonstrated high serum lactate was associated with higher mortality. Serial determination of serum lactate levels was a better predictor of poor outcome.

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PROFORMA:

NAME:

AGE:

SEX:

PLACE:

PRESENTING COMPLAINTS:

Cough & Cold

Fever

Difficulty In Breathing

Loose Stools

Vomiting

Urine Output

Convulsions

Altered Sensorium

EXAMINATION:

APPEARANCE
BREATHING
COLOUR
AIRWAY
RESPIRATORY RATE
TIDAL VOLUME
WOB
AIR ENTRY
ADDED SOUNDS
SPO2
HEART RATE
PULSE VOLUME

CRT
TEMP .GAP
BP
LIVER SPAN
URINE (hr)
AVPU
DEM
PERL
FIT / BLEEDING
INTERVENTION

GENERAL EXAMINATION

Anemia

Jaundice

Clubbing

Cyanosis

Pedal Edema

Lymphadenopathy

Nutrition

SYSTEMIC EXAMINATION :

CVS :

RS :

ABDOMEN :

CNS:

INVESTIGATIONS:

Complete Blood Count

Total count

Hb –

Platelet Count ----

Dc : N ____ L _____

Blood Urea :

Blood Sugar :

Serum Creatinine :

Serum Sodium :

Serum Potassium :

Serrum Bilirublin

SGOT,SGPT

PT,APTT,INR

Serum Lactate : Less Than 3 Hrs 24 Hrs

CRP:

ESR

ABG

Blood C/S :

Urine C/S :

Urine Routine :

CXR:

CSF Analysis

TREATMENT GIVEN:

OUTCOME:

Name	Age	Sex	Diagnosis	Count	Na+	K+	Anemia	Under Nutrition	Ventilation	Organ Dysfunction	Lact (0 -3 hr)	Lac (After 24 hrs	Outcome
Valasalal rahman	3 months - 12 months	Male	UTI	17500	136	4.2	Not Present	Present	Not Required	Not present	39.4	23	Survivor
Karuppasamy	3 months - 12 months	Male	Bronchopneumonia	16500	137	5	Present	Present	Required	Present	60.2	58.4	Non_Survivor
Hemavarshini	3 months - 12 months	Female	Meningitis	15000	143	4.4	Not Present	Present	Required	Present	57.8	51	Non_Survivor
Dharsan	3 months - 12 months	Male	UTI	10500	132	3.5	Present	Not Present	Not Required	Not present	32.4	27.6	Survivor
Nithish	13 months - 60 months	Male	Bronchopneumonia	13000	139	3.8	Present	Present	Required	Present	26.2	18.8	Survivor
Keerthana	13 months - 60 months	Female	Liver Abscess	31000	132	4.6	Not Present	Present	Not Required	Not present	24.8	16.6	Survivor
Rajim	3 months - 12 months	Female	Bronchopneumonia	18000	134	5.2	Present	Present	Required	Present	60.9	54.6	Non_Survivor
Salmon parvish	3 months - 12 months	Male	Meningitis	10900	140	4.2	Present	Present	Not Required	Present	31	23.4	Survivor
Santhoshkumar	13 months - 60 months	Male	Bronchopneumonia	16800	136	3.8	Present	Not Present	Not Required	Not present	41	24.6	Survivor
Rithika	13 months - 60 months	Female	Bronchopneumonia	12500	139	3.5	Not Present	Present	Required	Present	25.8	16	Survivor
Kishori	3 months - 12 months	Female	Bronchopneumonia	15600	140	3.6	Present	Present	Not Required	Not present	27.4	18.8	Survivor
Halubuisha	13 months - 60 months	Female	Bronchopneumonia	9900	137	4.2	Present	Present	Required	Present	29	21	Survivor
Shrikh Arsadh	13 months - 60 months	Male	Meningitis	13500	138	4.8	Not Present	Present	Not Required	Present	38	25.2	Survivor
Sridar	13 months - 60 months	Male	Bronchopneumonia	18000	143	5	Present	Present	Required	Present	64.6	52.8	Non_Survivor
Krishna moorthy	3 months - 12 months	Male	Bronchopneumonia	9800	138	3.6	Not Present	Not Present	Not Required	Not present	25.8	16	Survivor
Darika	13 months -	Female	Bronchopneumonia	7500	144	4.6	Present	Present	Not	Present	26.4	19.8	Survivor

	60 months								Required				
Basila	13 months - 60 months	Female	Bronchopneumonia	16000	144	3.8	Present	Present	Required	Present	72.4	66	Non_Survivor
Swathika	3 months - 12 months	Female	ADD	15600	143	3.2	Present	Not Present	Not Required	Not present	33.8	27.2	Survivor
Santhosh	3 months - 12 months	Male	ADD	7800	141	2.8	Present	Present	Required	Present	29.8	26.2	Survivor
Nithyarubini	13 months - 60 months	Female	Bronchopneumonia	8800	138	3.5	Present	Present	Not Required	Not present	22.8	16.4	Survivor
Narmatha	3 months - 12 months	Female	Bronchopneumonia	28000	135	3.8	Not Present	Not Present	Not Required	Not present	37.2	26.8	Survivor
Logesh	3 months - 12 months	Male	ADD	16000	137	4	Present	Present	Not Required	Present	25.6	19.2	Survivor
Sriragavan	3 months - 12 months	Male	Bronchopneumonia	14300	144	3.6	Present	Present	Required	Present	26.8	20.6	Survivor
Aslin	61 months - 144 months	Female	Meningitis	19000	142	4.4	Present	Present	Not Required	Present	76	71.8	Non_Survivor
Kathirvel	3 months - 12 months	Male	Bronchopneumonia	15600	138	3.8	Not Present	Not Present	Required	Present	28.8	20	Survivor
Imisha	3 months - 12 months	Female	Bronchopneumonia	16000	140	3.4	Present	Present	Required	Present	43.4	39.6	Non_Survivor
Adithyamathi	3 months - 12 months	Female	Bronchopneumonia	16500	138	4.2	Present	Present	Not Required	Not present	28.6	22	Survivor
Prem	3 months - 12 months	Male	Bronchopneumonia	15800	143	4.4	Present	Present	Required	Present	55.6	49.8	Non_Survivor
Babu	3 months - 12 months	Male	Bronchopneumonia	14200	144	3.8	Present	Not Present	Required	Present	62.4	60.2	Non_Survivor
Kavya	13 months - 60 months	Female	Bronchopneumonia	22000	137	4.2	Not Present	Present	Required	Present	49.8	45.2	Non_Survivor
Abirami	3 months - 12 months	Female	Bronchopneumonia	8900	142	3.8	Present	Not Present	Not Required	Present	25.6	19.2	Survivor
Siva	3 months - 12 months	Male	Bronchopneumonia	15300	144	3.5	Present	Present	Required	Present	58.8	51.4	Non_Survivor
Devika	61 months -	Female	ADD	17000	140	3	Present	Present	Not	Not present	64.2	58.8	Non_Survivor

	144 months								Required				
Suresh	13 months - 60 months	Male	Bronchopneumonia	13900	135	3.8	Not Present	Present	Required	Present	49.8	46.6	Non_Survivor
Poorani	3 months - 12 months	Female	Bronchopneumonia	14300	138	4.2	Present	Not Present	Required	Present	68	61.2	Non_Survivor
Kannamma	13 months - 60 months	Female	Bronchopneumonia	13800	140	3.5	Present	Present	Required	Present	63.2	59.4	Non_Survivor
Mahesh	3 months - 12 months	Male	ADD	8100	140	2.6	Present	Not Present	Not Required	Not present	28.2	21	Survivor
Arun	13 months - 60 months	Male	Meningitis	19100	135	4	Not Present	Present	Required	Present	49.8	45.2	Non_Survivor
Roopa	3 months - 12 months	Female	Bronchopneumonia	10200	136	5	Present	Present	Not Required	Not present	21	18.6	Survivor
Parvathi	13 months - 60 months	Female	Bronchopneumonia	14300	137	4.2	Not Present	Present	Required	Present	68.8	61	Non_Survivor
Raja	13 months - 60 months	Male	UTI	7900	139	4.8	Not Present	Not Present	Not Required	Not present	23	18.2	Survivor
Kumar	13 months - 60 months	Male	Bronchopneumonia	15600	142	3.8	Present	Present	Required	Present	51	45.6	Non_Survivor
Selvambal	3 months - 12 months	Female	Meningitis	16700	139	3.6	Present	Present	Required	Present	66.2	64.4	Non_Survivor
Pravin	61 months - 144 months	Male	Bronchopneumonia	10500	135	4	Present	Present	Not Required	Not present	31.2	24.6	Survivor
Kannan	3 months - 12 months	Male	ADD	18800	136	3.4	Not Present	Present	Not Required	Present	70.2	69.4	Non_Survivor
Deepak	13 months - 60 months	Male	Bronchopneumonia	13500	140	4.8	Present	Not Present	Required	Present	72.4	68.8	Non_Survivor
Devi	61 months - 144 months	Female	Bronchopneumonia	12000	138	4	Present	Present	Not Required	Not present	48.4	39.2	Survivor
Priya	13 months - 60 months	Female	Bronchopneumonia	13900	135	4	Not Present	Present	Not Required	Present	43.4	39.6	Non_Survivor
Naveen	13 months - 60 months	Male	ADD	22000	142	3.6	Present	Not Present	Not Required	Not present	28.6	22	Survivor
Senthil	61 months -	Male	Meningitis	16700	137	4.2	Present	Not	Required	Present	55.6	49.8	Survivor

	144 months							Present					
Murugan	13 months - 60 months	Male	Bronchopneumonia	13800	136	4	Not Present	Present	Not Required	Present	45.7	40.6	Non_Survivor
shanmugam	61 months - 144 months	Male	Bronchopneumonia	16000	138	4.6	Present	Present	Not Required	Not present	28.7	17.4	Non_Survivor
Fathima	61 months - 144 months	Female	Bronchopneumonia	16500	141	3.8	Present	Present	Not Required	Not present	49.8	45.2	Survivor
sudalai	61 months - 144 months	Male	Bronchopneumonia	7900	135	3.8	Not Present	Present	Required	Present	21	18.6	Survivor
Pogal	3 months - 12 months	Male	ADD	13900	138	4.2	Present	Not Present	Required	Present	68.8	61	Survivor

OBJECTIVES OF THE STUDY

1. To determine the association between serum lactate level and mortality in pediatric septic shock.
2. To determine whether serial determination of serum lactate level is a predictor of outcome in pediatric septic shock.
3. To determine the association between organ dysfunction, presence of anemia, malnutrition, diagnosis and outcome in pediatric septic shock.

MATERIAL AND METHODS :

50 Children between 3 months to 12 years admitted with clinical diagnosis of septic shock were included. Clinical diagnosis of septic shock was made based on pediatric assessment triangle – temperature instability with warm or cold shock or hypotensive shock. Following clinical data were recorded in proforma after obtaining consent from the parents–age, sex, clinical history, examination findings, duration of stay, Treatment after admission in PICU, vital parameters, complete blood count, peripheral smear, blood culture, urine analysis, urine culture, blood urea, serum electrolytes, serum creatinine, serum bilirubin, serum alanine transaminase, Blood gas analysis was obtained in all cases. Prothrombin time, activated partial thromboplastin time was measured if clinically indicated. CSF analysis was done in children with clinical suspicion of CNS infection. Lactate in

arterial blood was measured at 0 to 3 hours and after 24 hours of admission. Lactate level was estimated using enzymatic method.

RESULTS

The odds ratio, positive predictive value and negative predictive value for the cut off value of lactate ≥ 41 mg/dl measured at 0 to 3 hours are 119.6, 82.1% and 96.2% respectively. These were statistically significant. The odds ratio, positive predictive value for the cut off value of lactate ≥ 39.2 mg/dl measured at 24 hours are 65.33, 85.1% and 96.4% respectively. These were statistically significant.

- Lactate measured at 0 to 3 hours and at 24 hours was significantly high in non survivors. Apart from serum lactate, presence of organ dysfunction and under nutrition were significantly associated with poor outcome.
- Initial serum lactate value ≥ 41 mg/dl (4.55 mmol /L) and serum lactate value of ≥ 39.2 mg /dl (4.35 mmol /l) at 24 hours were significant predictors of poor outcome in children with septic shock.