Serum Cortisol level in children with catecholamine dependent shock – A prospective observational study

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A Dissertation submitted to THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY In partial fulfilment of the regulations for the award of degree of M.D DEGREE (PEDIATRICS) BRANCH VII

INSTITUTE OF SOCIAL PEDIATRICS
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APRIL 2017

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation / thesis entitled "Serum cortisol level in children with catecholamine dependant septic shock– A prospective observational study" is a bonafide and genuine research work carried by me, **DR.VIJAYA BHARATHI.E**, under the guidance of **Prof.S. SHANTHI, MD.,DCH,** Professor in Department of pediatrics.

The dissertation is submitted to **The Tamilnadu Dr.M.G.R Medical University** towards the partial fulfillment of the rules and regulations for the **M.D Degree Examination - BRANCH VII - in Pediatrics**.

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CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"Serum cortisol level in children with catecholamine dependent septic shock – A prospective observational study"**is a bonafide record of work carried out by **DR.VIJAYA BHARATHI.E,**, in the Department of paediatrics, Government Stanley medical college, under my guidance and supervision during the period of her post graduate study for M.D. paediatrics from MAY 2014 to March 2017.

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This to certify that the dissertation titled **"Serum cortisol level in children with catecholamine dependent septic shock – A prospective observational study"**is a bonafide record of work carried out by **DR. E.VIJAYABHARATHI.E**, in the Department of paediatrics under our direct supervision and guidance, during the academic year 2014 -2017 submitted to **The Tamilnadu Dr.M.G.R Medical University, Chennai** in partial fulfillment of the requirement of the award for the degree of **M.D BRANCH VII (PEDIATRICS).**

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ACKNOWLEDGEMENT

It is with immense pleasure and gratitude that I thank **Dr. ISAAC CHRISTIAN MOSES M.D.,FICP.,FACP,THE DEAN, STANLEY MEDICAL COLLEGE** for bestowing me the permission and privilege of presenting this study and for enabling me to avail the institutional facilities.

It is with great pleasure that I express a deep sense of gratitude to my teacher and **Guide**, **Prof. S.SHANTHI MD., DCH.,**Professor , department of pediatrics, for her valuable guidance and support during the preparation of this dissertation and also inspiring me at every step of this study, for without her this study wouldn't be possible.

I express my gratitude to my **Co- guide, Dr.Ekambaranath M.D,** Assistant Professor of PICU for his valuable help and guidance throughout this study.

I am very grateful to all my chiefs, **Prof.Dr vivekanandan Prof.Dr.Lakshmi M.D, DCH, Prof. Dr. Devimeenakshi M.D, DCH and Prof. Dr Subramanian M.D,DCH** for their valuable guidance and motivation.

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I am extremely thankful to **Dr.Elango M.D, DCH** Medical Registrar, for his valuable suggestions and guidance during this study.

I sincerely thank my Assistant Professors **Dr.P.Venkatesh M.D, Dr.Radhika M.D, Dr.Raja M.D, Dr.Vinoth M.D, Dr.Kumar DCH** , **Dr.Sankara Narayanan M.D , Dr.Parveen kumar M.D , Dr. Senthilkumar and Dr Rajesh** for their valuable support throughout the course of this study.

I thank all the post graduates in the Department of Pediatrics in our Stanley Medical College who has helped me and it was an immense pleasure working with all.

Finally I wish to express my whole-hearted thanks to all the Emergency and PICU nurses and all the patients who participated in the study.

Dr.E.VIJAYA BHARATHI

TABLE OF CONTENTS

LIST OF TABLES:

LIST OF FIGURES:

ABBREVATIONS AND ACRONYMS:

RAI - RELATIVE ADRENAL INSUFFICIENCY

AI - ADRENAL INSUFFICIENCY

PICU - PEDIATRIC INTENSIVE CARE UNIT

CL - CORTISOL LEVEL

ACTH - ADRENOCORTICOTROPHIC HORMONE

HDL - HIGH DENSITY LIPOPROTEINS

CRT - CAPILLARY REFILLING TIME

SVR - SYSTEMIC VASCULAR RESISTANCE

CPAP - CONTINOUS POSITVE AIRWAY PRESSURE

INOS - INDUCIBLE NITRIC OXIDE

SD - STANDARD DEVIATION

INTRODUCTION

Severe sepsis and Septic shock in paediatric intensive care unit in hospitals worldwide have emerged as an important cause of mortality and morbidity and a challenge even to many developed countries. The key to have a better outcome in children with septic shock is the early recognition of shock, starting aggressive fluid therapy, early initiation of first dose antibiotic and to start appropriate inotropes when warranted.

In many children who are admitted with septic shock, we encounter fluid and catecholamine resistant shock, and this may be due to adrenal insufficiency. Though occurrence of absolute adrenal insufficiency is rare, relative adrenal insufficiency is common with children with septic shock.

There are many data in adults that suggest early treatment with glucocorticoids improves the outcome. There are not enough studies in children on the magnitude of adrenal insufficiency. Absolute and relative adrenal insufficiencies (RAI) are determined

by basal cortisol (CL) level. To assess the adrenal reserve, low dose ACTH stimulation test may be used.

In non-critically ill patients a basal cortisol level of more than 18 mcg/dl (500nmol/lt) is considered to have normal adrenal function[1-5]. Several authors to define relative adrenal insufficiency used random cortisol level.Marik et al [6] considered random level <500 nmol/l inappropriate to define RAI in critically ill patients and used a cutoff of 690 nmol/dl(25mcg/dl) for defining adrenal insufficiency. The prevalence of adrenal insufficiency was 61% in his study . Sam et al[7] and Moran et al[8] defined the basal CL level as 550 and 500 respectively and had a prevalence rate of about 30%. In other studies by Offner et al[9] and Rydvall et al[10] also defined random cortisol level less than 500nmol/lt as adrenal insufficiency. There are very few studies in our setup to determine the prevalence of adrenal insufficiency

In order to identify prevalence of adrenal insufficiency and to define the need for steroid replacement in children suffering

from septic shock, we designed this prospective observational study. In this study we measured the basal serum cortisol level in children with catecholamine dependent shock and studied its association with the clinical outcome in terms of need for inotropic support, ventilator support, length of stay in hospital and mortality in children.

AIMS AND OBJECTIVES

Primary outcome measure:

To identify the prevalence of **Adrenal insufficiency by measuring Serum cortisol level with catecholamine dependant septic shock in children of age group 1 Month – 12 years.**

Secondary outcome measure:

To analyse the clinical outcome of septic shock in terms of

- Need for and duration of ventilator support,
- Duration of inotropic support
- Length of hospital stay and
- Mortality

REVIEW OF LITERATURE:

SEPSIS:

History of sepsis dates back to the era of Hippocrates (460-370BC), who first coined the word sepsis which was derived from a Greek word sepsi which means “make rotten”. Ibnsina found that there was a relation between blood putrefaction and fever. Marcus terentius varro, the ancient roman scholar and writer (116 bc–27 bc), quoted as noting that “small creatures, invisible to the eye, fill the atmosphere, and breathed through the nose cause dangerous diseases.”

The modern view of sepsis was proposed by Ignazsemmelweiz, who was an obstetrician in general, hospital, Vienna. He noticed that there were many puerperal deaths and he was able to bring down the mortality rate in their hospital by simply hand washing techniques.

It was Louis Pasteur who discovered that there was tiny microscopic organism, named it as bacteria / microbes which may be the reason for the disease. Joseph Lister a surgeon at Glasgow Royal Infirmary studied the death that occurred due to sepsis in

post-operative amputation patients. From the data that he collected and correlating it with previous work done by Semmelweiz and Pasteur he introduced in antiseptic technique and by this he was able to bring down mortality in their hospital drastically.

A German physician H. Lennhartz was the person who changed the concept of blood putrefaction to the newer concept of disease and its consequence caused due to bacteria. Later it was his student Hugo Schottmuller in 1914 gave the modern definition of sepsis.“Sepsis is present if a focus invades the bloodstream in such a way that this cause subjective and objective symptom’. Also added “The therapy should not be directed against the bacteria in the blood but against the released bacterial toxins”.

In pre antibiotic era there were many deaths and mostly these patients had low blood pressure which was termed as septic shock.

It was also observed by Asbough and his colleagues that the patients with sepsis developed severe lung disease which they called as adult respiratory distress syndrome and this was associated with increased mortality. They finally drew a conclusion

that there was some inflammatory reaction that occurred in various parts of the body as a result of bacterial invasion.

Roger C.Bone[11], US-American ICU specialist, in 1989 gave a definition for sepsis as "sepsis is defined as an invasion of microorganisms and /or their toxins into the bloodstream , along with the organism's reaction against this invasion".

In the past centuries, a variety of definition for sepsis was proposed in an attempt to understand sepsis clinically better. In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) jointly published the consensus definitions of sepsis. In this they described systemic inflammatory response syndrome criteria and they gave definition for sepsis, severe sepsis, septic shock and multiple organ dysfunction syndrome.

Surviving sepsis campaign ever since its inception in 2002 has been committed to reducing mortality in severe sepsis and septic shock worldwide.

DEFINITION

Goldstein B Giroir et al[12] in international paediatric sepsis consensus conference modified the definition of SIRS and sepsis. About 20 experts from five nations convened so as to modify the consensus in adults appropriate for neonate, infant, child and adolescence, that is according to different age group.

INTERNATIONAL CONSENSUS DEFINITION FOR PAEDIATRIC SEPSIS:

INFECTION:

Suspected or proven infection or a clinical syndrome associated with high probability of infection

SIRS :

Two of 4 criteria, 1 of which must be abnormal temperature or abnormal leukocyte count:

1. Core temperature >38.5°C (101.3°F) or <36°C (96.8°F) (rectal, bladder, oral, or central catheter)

2. Tachycardia: Mean heart rate >2 SD above normal for age in absence of external stimuli, chronic drugs or painful stimuli *or* Unexplained persistent elevation over 0.5-4 hr *Or* In children <1 yr old, persistent bradycardia over 0.5 hr (mean heart rate <10th percentile for age in absence of vagal stimuli, β-blocker drugs, or congenital heart disease)
3. Respiratory rate :>2 SD above normal for age or acute need for mechanical ventilation not related to neuromuscular disease or general anesthesia
4. Leukocyte count elevated or depressed for age (not secondary to chemotherapy) or >10% immature neutrophils

Sepsis:

SIRS plus a suspected or proven infection

Severe sepsis:

Sepsis plus 1 of the following:

1 .Cardiovascular organ dysfunction, defined as:

• Despite>40 mL/kg of isotonic intravenous fluid in 1 hr:

• Hypotension <5th percentile for age or systolic blood pressure <2 SD below normal for age*or*

• Need for vasoactive drug to maintain blood pressure*Or*

• 2 of the following:

• Unexplained metabolic acidosis: base deficit >5 mEq/L

• Increased arterial lactate: >2 time's upper limit of normal

• Oliguria: urine output <0.5 mL/kg/hr

• Prolonged capillary refill: >5 sec

• Core to peripheral temperature gap >3°C (5.4°F)

2. ARDS as defined by the Presence of a PaO2/FIO2 ratio ≤300 mm Hg, bilateral infiltrates on chest radiograph, and no evidence of left heart failure or

Sepsis plus 2 or more organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic)

SEPTIC SHOCK:

Sepsis plus cardiovascular organ dysfunction as defined above.

MULTIPLE ORGAN DYSFUNCTION SYNDROMES:

Presence of altered organ function such that homeostasis cannot be maintained without medical intervention

EPIDEMIOLOGY OF SEPSIS AND SEPTIC SHOCK:

The prevalence of sepsis, severe sepsis and septic shock in United States is estimated to be 40000 every year with annual incidence of 056 cases per 1000 population. Infants had the highest incidence of severe sepsis compared to older age group with a decreasing trend in older age groups. In this population more than 40 percent were due to respiratory infections and some were due to primary bacteraemia.

Hartmann et al[13] conducted retrospective observational cohort study in children in age group of 0 to19 yrs. and concluded that there was a rising trend in sepsis mainly contributed by neonatal sepsis

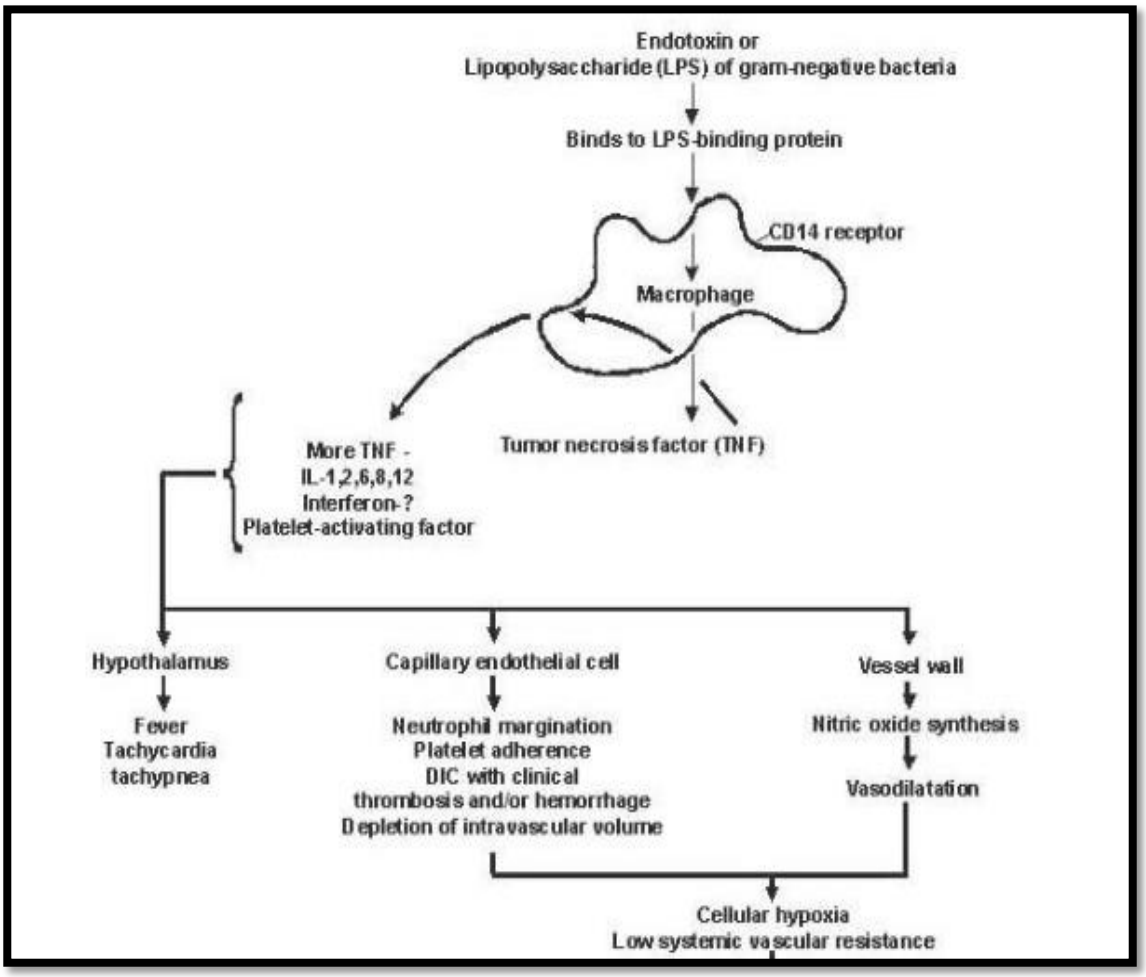
In another study done by Balamuth et al[14] an observational cohort study in children younger than 18 yrs. in U.S from 2004 to 2014 , he concluded that though there was an increase in prevalence of sepsis, the resource utility and mortality has come down drastically.

Data from Indian study differs from western literatures. S.Todi et al[15] in a multicentric, prospective, observational study, conducted in four intensive therapy units in India, concluded that mortality was high in Indian setup than in west and more viral and parasitic infections and less gram positive infection encountered compared to western countries

PATHOPHYSIOLOGY OF SEPSIS AND SEPTIC SHOCK:

Sepsis is caused due to dysregulated inflammatory response to infection elsewhere in the body. Effects of sepsis ranges from bacterial invasion to circulatory collapse to multiorgan failure and death. Earlier studies on sepsis showed that toxin due to gram negative organism play a role in pathophysiology of sepsis. But recent studies shows there is an increasing trend in gram positive organism, some fungi and even parasite are responsible for the effect.

PATHOGENESIS OF SEPSIS AND MODS



There are many mediators released by neutrophils and macrophages that are responsible for inflammation and coagulation abnormalities. The extrinsic coagulation is activated by cytokines and they inhibit fibrinolysis. The cytokines activate the extrinsic coagulation cascade and inhibit fibrinolysis. These processes result in micro vascular thrombosis potential factor producing organ dysfunction.

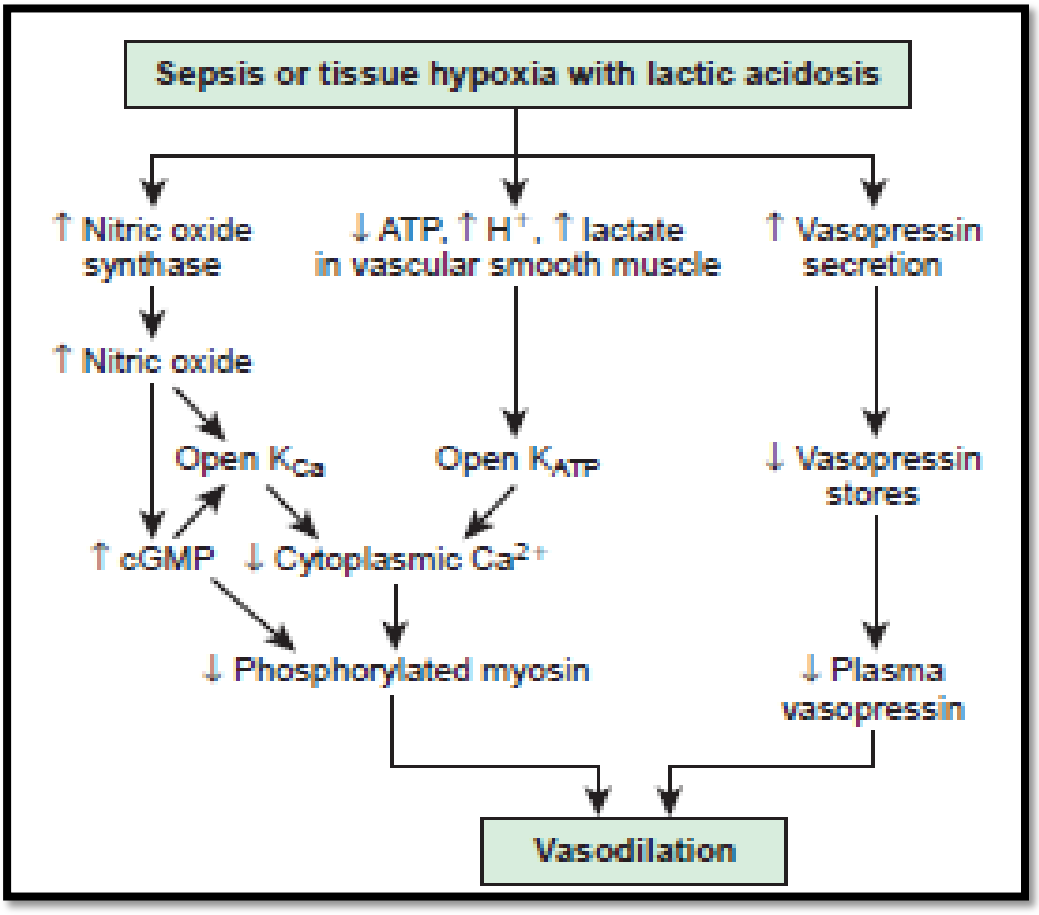
Septic shock:

Septic shock results as the vascular tone is lost in sepsis and it is no longer able to constrict adequately to maintain the blood pressure. Three factors play a role in septic shock:

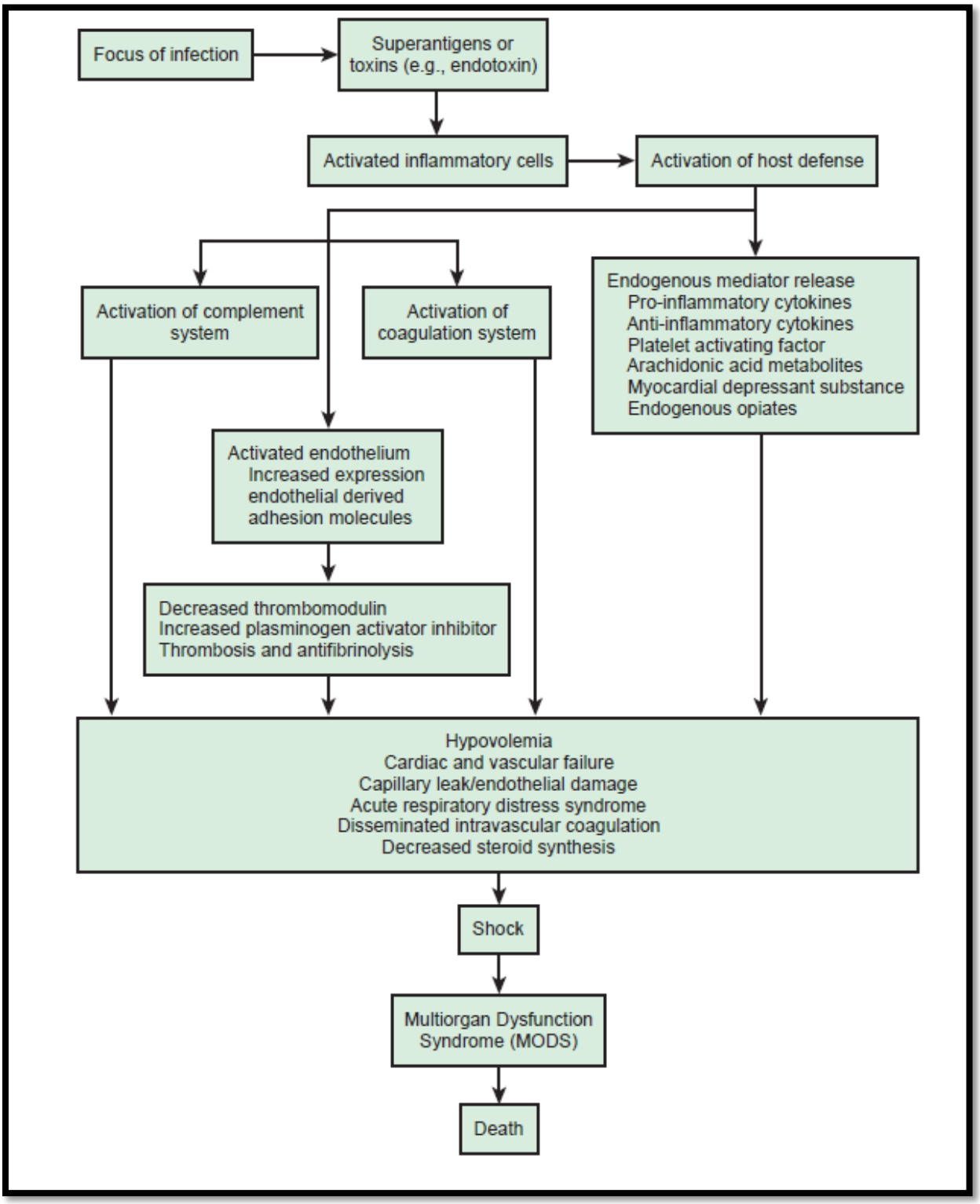
- High level of lactic acid
- Suppress vasopressin release from pituitary
- Excess nitric oxide is produced by endothelial cells due to sepsis

Death usually result from multiorgan failure rather than single system involvement

MECHANISM OF VASODILATORY SHOCK



HYPOTHETICAL PATHOPHYSIOLOGY OF SEPSIS AND SEPTIC SHOCK AND MULTIORGAN DYSFUNCTION



ADRENAL INSUFFICIENCY IN SEPTIC SHOCK:

In sepsis and in other critically ill status, the body tries to adapt to stress by elevating blood cortisol level. Relative adrenal insufficiency occurs in septic shock and other critical illness and primary insufficiency is very rare. In primary adrenal insufficiency there is destruction of adrenal cortex where as in relative adrenal in sufficiency there is transient decrease in adrenal reserve due to adrenal exhaustion.

In critical illness and septic shock, cortisol synthesis can be impaired by

- Necrosis of hypothalamus or pituitary gland[16].
- Bilateral necrosis or haemorrhage of the adrenals[17].
- Many drugs that are used during critical illness or sepsis will hinder their synthesis like etomidate,ketoconazole fluconazole
- Certain drugs causes increase in metabolism of cortisol like rifampicin, clarithromycin, phenytoin phenobarbitone, ketoconazole
- Cortisol synthesis impaired by inflammatory cytokines

- There is Impaired activity of glucocorticoid receptor
- Decreased production may also be due to substrate deficiency. Cortisol synthesized from cholesterol and there are decreased HDL levels in sepsis [18].
- Substrate deficiency may lead to decreased cortisol synthesis in sepsis and thereby there is decreased supply to the site of inflammation [19].

SIGNS OF SEPTIC SHOCK:

During early stages of shock, since the peripheral perfusion appears good, it is very difficult to identify the signs of shock. Signs are often subtle may be due to sepsis like fever or hypothermia , increased or decreased WBC count and other abnormalities often noted are metabolic acidosis and respiratory distress.

Clinically, child may have,

- Altered level of consciousness
- Effortless tachypnea
- Tachycardia
- Bounding peripheral pulses

- Brisk or delayed CRT
- Skin- warm or flushed / cold or mottled or pale
- Blood pressure-Wide pulse pressur or
  - Narrow pulse pressure or
  - Normotensive.
- Oliguria
- Other finding are fever / petechiae / purpuric rash

In septic shock

Preload	decreased
contractility	Normal/ decreased
after load	variable

COMPENSATORY MECHANISM:

There are many compensatory mechanisms, develop in an attempt to maintain O2 delivery to vital organs.

They are

- Tachycardia
- Increased SVR

- Increased contractility
- Increase in venous smooth muscle tone

There is an increase in SVR which tries to maintain blood pressure, as cardiac output decreases as a result of shock. As the shock progresses SVR cannot increase still further and O2 supply to all vital organs are affected and this result in metabolic acidosis and end organ damage occurs. Since myocardium also receives inadequate O2, myocardial dysfunction occurs and finally leads to irreversible damage, cardiovascular collapse and cardiac arrest.

ETIOLOGY OF SEPTIC SHOCK:

Sepsis may be caused by bacteria, viruses, fungi and parasites.

Causes: Bacterial causes vary according to age, they are as follows:

Early-onset neonatal sepsis;

Streptococcus agalactiae,

Escherichia coli,

Haemophilusinfluenza, and

Listeria monocytogenes

Late-onset neonatal sepsis:

coagulase-negative Staphylococcus,

Staphylococcus aureus,

E coli,

Klebsiella species,

Pseudomonas aeruginosa,

Enterobacter species,

Candida species,

S agalactiae,

Serratia species,

Acinetobacter species, and

Various anaerobes

Infants and children:

Streptococcus pneumoniae,

Neisseria meningitidis

H influenzae type b (Hib),

Salmonella species.

Malaria,

(Plasmodium falciparum is a frequent cause of SIRS in infancy).

In infancy and childhood , sepsis is caused by mostly the same pathogen though there an decrease in infection encapsulated organism as the children gets older may be with immune response to polysaccharide improves with age

Risk factors:

Host factors such as underlying illness or pathology may predispose to infection:

- Congenital heart disease
- AIDS
- Children with hemoglobin SS
- significant burns
- children who are hospitalized (particularly in the intensive care unit [ICU])
- indwelling devices or prosthetic material

CLASSIFICATION OF SHOCK:

Shock is broadly classified as, hypovolemic, distributive and cardiogenic

HYPOVOLEMIC SHOCK:

Hypovolemic shock result from volume loss and has absolute intravascular deficiency of blood volume. In sepsis, hypovolemic shock occurs due to third space loss or capillary leak due to inflammatory mediators. Due to decreased preload there is decrease in stroke volume and cardiac output.. This is compensated at early stage by tachycardia, increased systemic vascular resistance, and increased cardiac contractility.

CARDIOGENIC SHOCK;

In cardiogenic shock, intravascular volume is normal or increased .End diastolic volume is also increased. Due to decreased myocardial contractibility, there is reduced stroke volume and has compensatory increase in heart rate and systemic vascular

resistance. Any shock will finally cause impaired myocardial function.

DISTRIBUTIVE SHOCK:

Inadequate organ/ tissue perfusion due to inappropriate distribution of blood volume is known as distributive shock.

Common forms- septic shock ,

anaphylactic shock ,

neurogenic shock

In contrast to other types of shock, there is high cardiac output and low systemic vascular resistance in distributive shock

SEPTIC SHOCK:

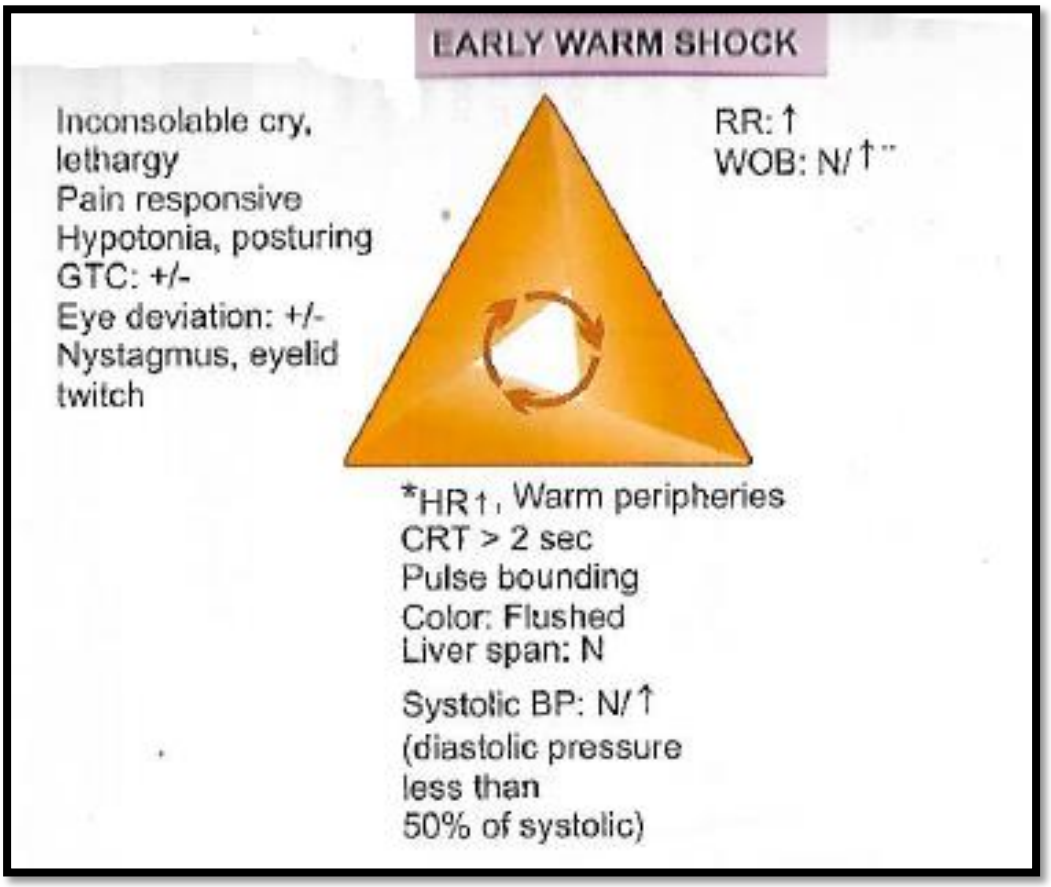
Septic shock is severe sepsis with presence of hypo perfusion. It is the most common of distributive shock

In septic shock, there is relative hypovolemic due to vasodilatation which cause pooling of blood in venous system.

Sepsis causes decreases or increased SVR leading to inadequate blood flow. Septic shock is due to inflammatory mediators released as a result of host response to infectious organism or their toxins.

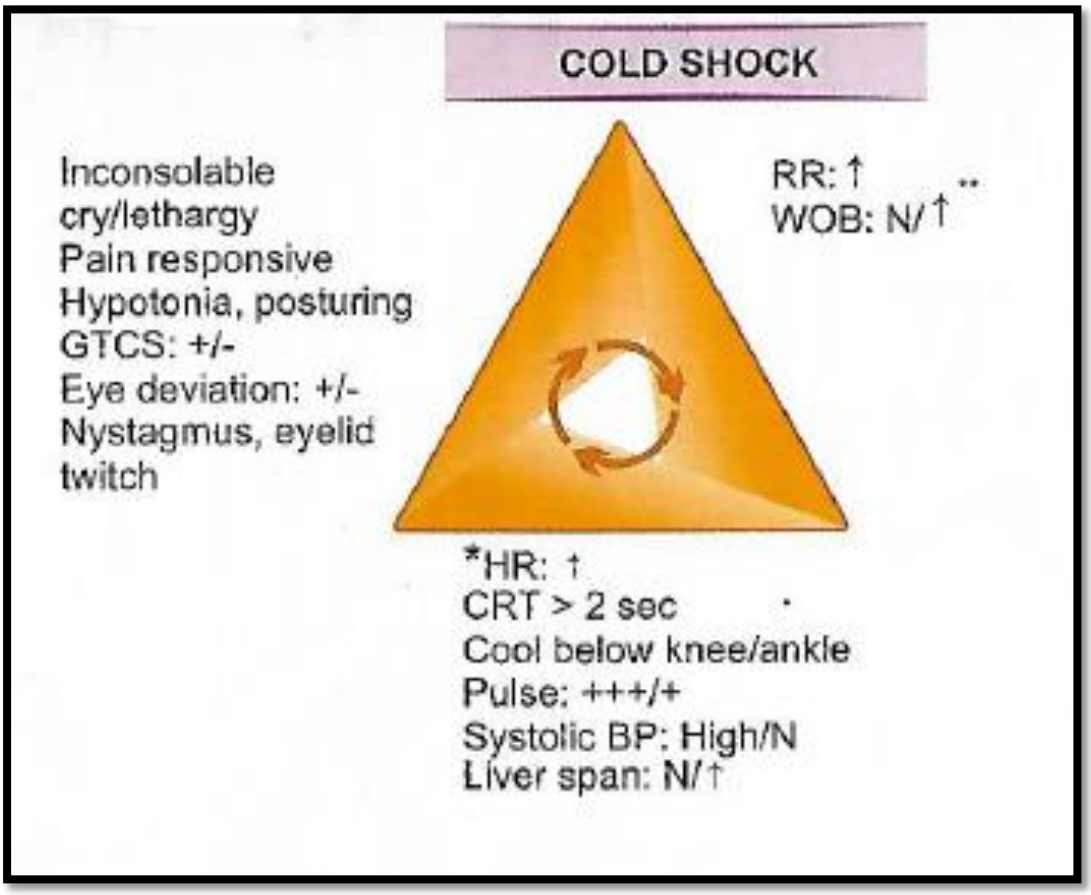
WARM SEPTIC SHOCK

In the early stages of septic shock, there is low SVR and has hyper dynamic phase with increased blood flow to the skin which is called as Warm septic shock. This produces warm extremities and bounding peripheral pulses. In order to meet the greater metabolic demands of organs and tissues and to maintain adequate oxygen delivery, cardiac output increases.

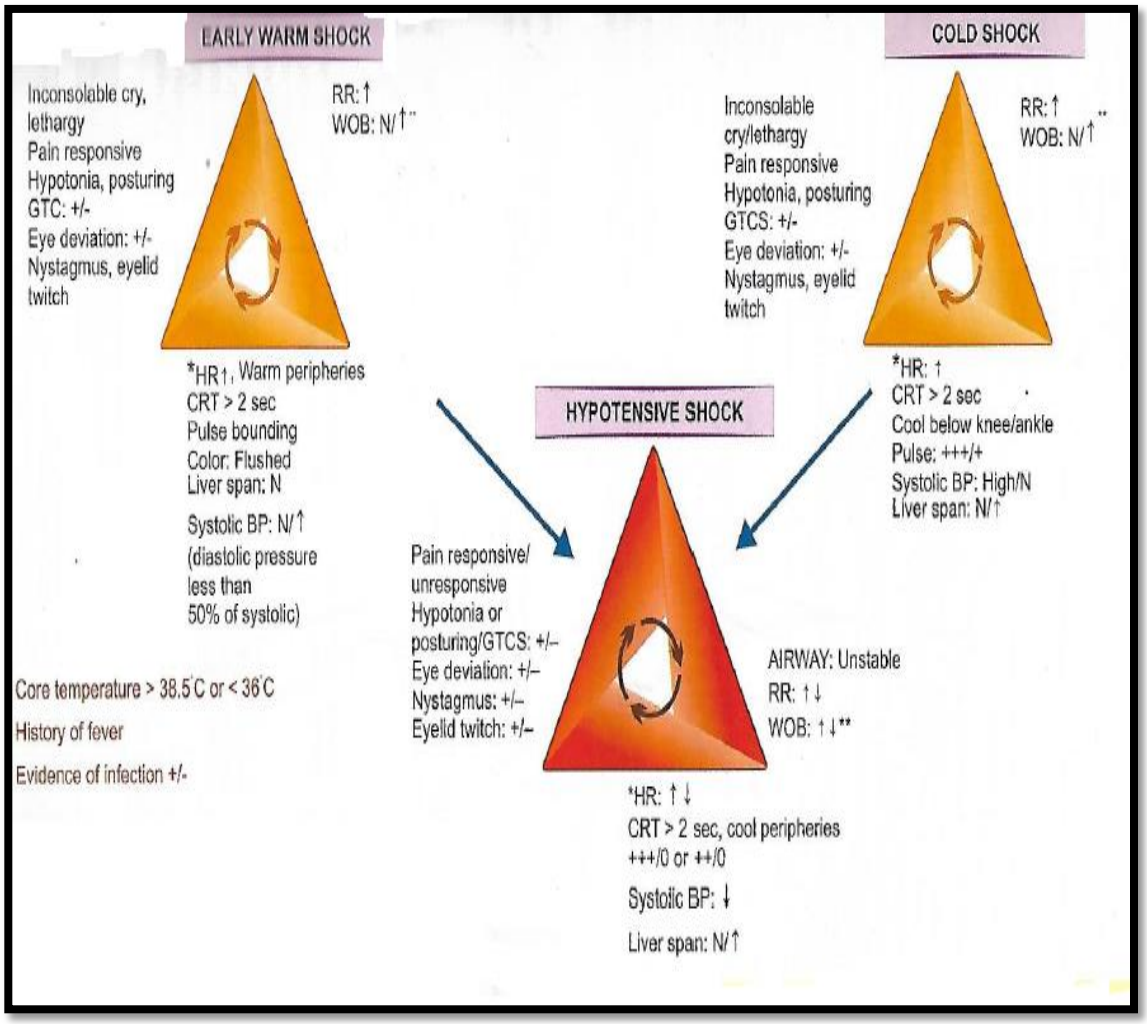


COLD SEPTIC SHOCK:

AS the shock progresses , compensatory mechanism fails and in response to many inflammatory mediators ,cardiac output falls , and there is increased SVR, leading to in adequate blood flow to skin causing cold peripheries and weak pulse, this is called as cold septic shock



HYPOTENSIVE SHOCK:



DIAGNOSIS OF SEPTIC SHOCK:

Diagnosis is mainly based on a

Thorough history

Physical examination

An infectious etiology should be sought

Culture of clinically appropriate specimens should be done

Noninvasive monitoring

Pulse oximetry, capnography, Near infra-red spectroscopy

Invasive monitoring

Central venous pressure,

Arterial blood pressure

LABORATORY FINDINGS:

1 Complete hemogram:

Hematologic abnormalities may include

Anemia.

Thrombocytopenia,

Elevated neutrophil count

Increased immature forms (i.e., bands,

myelocytes, promyelocytes)

vacuolation of neutrophils, toxic granulations, and

Dohle bodies may be seen

Neutropenia or leukopenia may be an ominous sign of overwhelming Sepsis.

2 METABOLIC ABNORMALITIES:

Glucose dysregulation, may manifest as

Hyperglycemia

Hypoglycemia.

3 ELECTROLYTEABNORMALITIES:

Hypocalcaemia,

Hypoalbuminemia,

Metabolic acidosis.

4 RENAL DYSFUNCTION:

Blood urea

Serum creatinine

5 HEPATIC FUNCTIONS MAY ALSO BE ABNORMAL.

6 COAGULATION ABNORMALITIES:

Prolonged prothrombin and Partial thromboplastin times,

Reduced serum fibrinogen level,

Elevations of fibrin split products

7 IMPAIRED OF OXYGENATION AND VENTILATION: (IN ARDS OR PNEUMONIA)

Decreased arterial partial pressure of oxygen [Pao2]

Increased arterial partial pressure of carbon dioxide [Paco2]

8 BLOOD LACTIC ACID LEVEL

Noted in all forms of shock

Indicates poor tissue oxygen delivery

Done to assess the severity of shock

Monitor response to fluid therapy

9 MEASUREMENT OF SVo2

Measured by cooximetry. Reflects decrease in oxygen delivery Clinically manifested by increased lactic acid production. Measured from pulmonary artery catheter Other sites are used as surrogate measures are right ventricle, right atrium, SVC or IVC.

10 ADRENALINSUFFICIENCY:

Basal serum cortisol can be measured

TREATMENT OF SEPTIC SHOCK:

In children with septic shock, management in first hour of arrival is the key to good prognosis .There are many studies worldwide, stating that early recognition of shock and aggressive treatment in early hours of arrival in Emergency department has a favourable outcome (HanYYetal)

Aggressive fluid therapy, early intubation, appropriate inotropes in fluid refractory shock and hydrocortisone if adrenal insufficiency is suspected are the main steps in management in children with septic shock. Also correction of metabolic abnormalities and administration of antibiotic within first hour is also important

Dellinger et al[(20)] in International guidelines for management of severe sepsis and septic shock update in 2012, states that recommendation specific for paediatric patients were for severe sepsis include oxygen therapy using face mask ,high flow nasal cannula oxygen, or nasopharyngeal peep if respiratory distress and hypoxemia ,use of physical examination therapeutic endpoint such

as capillary refill, for septic shock; for hypovolemic in septic shock ,the use of crystalloids to deliver a bolus of 20 ml /kg over 5 to 10 mts: inotropes and vasodilators for low cardiac output states with elevated systemic vascular resistance and only in suspected or proven adrenal insufficiency , hydrocortisone is indicated.

SPECIAL CONSIDERATIONS IN PEDIATRICS AS PROPOSED BY SURVIVING SEPSIS CAMPAIGN:

INITIAL RESUSCITATION

1 **Airway management**

Respiratory distress and hypoxemia

Face mask oxygen,

High flow nasal cannula oxygen

Nasopharyngeal CPAP

Mechanical ventilation

ECMO in refractory septic shock and respiratorydistress.

2 FLUID RESUSCITATION:

If central line is not accessible then , immediate peripheral intravenous or intraosseous access can used for fluid resuscitation and inotrope infusion

Hypotensive children:

Fluids used may be

Isotonic crystalloids Boluses of up to 20 mL/kg crystalloids over 5-10 minutes can be given

Start inotropic support , if hepatomegaly or rales appears

Non hypotensive children:

Boluses are given over 20 minutes.Blood transfusion is considered superior to crystalloids or albumin boluses.

Child is monitored for reversal of hypotension .During fluid administration, always monitor heart rate, skin temperature (warm or cold) , whether peripheral pulses felt, capillary refilling time , urine output and level of consciousness.

Pulmonary edema is the most frequent complication during the fluid therapy. If cardiogenic pulmonary edema develops, then, the rate and volume of fluid infused are reduced and inotrope is started depending on the type ofshock. And if non cardiogenic pulmonary edema develops, child may be connected to mechanical ventilator support.

3 INOTROPE/VASOPRESSORS/VASODILATOR

In children with septic shock who do not respond to fluid resuscitation can be started on inotropes .Inotropes are started according to type of shock warm or cold shock or normotensive shock.

Clinically it is very difficult to assess the type of shock whether it is vasoidlatory or vasoconstrictory shock. It can be assessed by cardiopulmonary assessment and deriving the physiological status.

Warm septic shock:

In children with fluid unresponsive, vasodilatory(warm) septic shock with poor perfusion or hypotension, the vasoactive agent of choice is Norepinephrine. By increasing the SVR, it raises the diastolic blood pressure by its potent α- adrenergic vasodilatoryeffect. It also causes increase in contractility without increase in heart rate. In Norepinephrine refractory shock, vasopressin infusion may be usefulCold septic shock

In cold septic shock, epinephrine is the vasoactive agent of choice. At a lower infusion rate, epinephrine has a β

adrenergic effect, thereby decreasing SVR. But at higher infusion rate, due to its α adrenergic, it increases the SVR. Predominant α adrenergic action is achieved by infusing epinephrine at a range of ≥0.3 mcg/ kg/mt.

Another alternative for cold septic shock is a combination of dobutamine and norepinephrine. The excessive decrease in SVR by the action of dobutamine is counterbalanced be norepinephrine infusion and there by achieve better splanchnic perfusion

VASOACTIVE THERAPY IN SHOCK

CLASS	**MEDICATION**	**EFFECT**
INOTROPES	Dopamine Epinephrine Dobutamine	Increase heart rate, contractility and has variable effect on SVR
PHOSPHODIESTERASE	Milrinone Inamrinone	Decrease SVR, Improve contractility and coronary blood flow
VASODILATORS	Nitroglycerin Nitroprusside	Decrease SVR and venous tone

VASOPRESSORS	Epinephrine (>0.3mcg/kg/mt) Norepinephrine Dopamine (10 mcg/kg/mt) vasopressin	Increase SVR Increase contractility

4 ANTIBIOTICS:

Empiric antibiotic should be given immediately after obtaining blood for cultures.

5 GLYCEMIC CONTROL:

Control of hyper glycaemia as in adults is important. Glucose with insulin infusion may be given. Hypoglycemia should also be monitored regularly

6 CORTICOSTEROIDS:

In children with fluid refractory, catecholamine resistant septic shock and suspected case of adrenal insufficiency, Hydrocortisone 2 mg / kg may given

7 BLOOD PRODUCT AND PLASMA THERAPIES:

Hemoglobin levels are targeted at 10 g/dl during resuscitation with low superior vena cava oxygen saturation shock of <70%

similar to adults. A lower hemoglobin target can be targeted after recovery from shock and hypoxemia

Platelets according to adult guidelines

Sepsis-induced thrombotic purpura disorders, including, secondary thrombotic microangiopathy, thrombotic thrombocytopenic purpura and progressive disseminated intravascular coagulation in children in septic shock may be corrected using plasma therapies.

8 SEDATION / ANALGESIA

In critically ill mechanically ventilated patients, sedation may used

9 DRUG TOXICITY:

As these children have greater risk of drug toxicity due to reduced drug metabolism in sepsis, monitoring for drug toxicity is mandatory

10 NUTRITION

Enteral feeding or parental feeding can be given to children depending on the severity

11 DIURETICS

In order to prevent fluid overload aftershock has been corrected, diuretics may be used. If unsuccessful, intermittent dialysis or continuous venovenous hemofiltration may be used

12 OTHERS

There is no recommendation on the use of DVT prophylaxis, stress ulcer prophylaxis or protein c and activated protein concentrate in children as in adults

Therapeutic end points that should be achieved:

- Normal heart rate / pulse rate for age
- Normal respiratory rate for age
- Normal blood pressure for age
- Warm extremities
- Capillary refill time < 2 secs
- No difference between central and peripheral pulses
- Liver span normal for age
- urine output > 1 ml/ kg/hr
- Normal mental status
- ScvO2 saturation≥70%
- Cardiac index between 3.3 and 6.0 L/min/m2

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NORMAL

APPEARANCE
Alert,
Tone and posture: N
Eyes: MP
EOM: N/PERL

BREATHING
RR: N (for age)
WOB: N
Color: N

CIRCULATION
HR: N (normal for age), Perfusion: N
Liver span: N
BP: N, PP: 30–40 mm Hg

NORMAL VITAL SIGNS FOR AGE

Age (kg)	Respiration	Heart rate	SBP
Newborn (3.5)	30–60	90–180	50–70
6 month (7)	24–40	85–170	65–106
1 year (10)	20–40	80–140	72–110
3 year (15)	20–30	80–130	78–114
6 year (20)	18–25	70–120	80–116
8 year (25)	18–25	70–110	84–122
10 year (30)	16–20	65–110	90–130
12 year (40)	14–20	60–110	94–136

STEROID THERAPY IN SEPTIC SHOCK

Steroids may have beneficial effect in improving hemodynamic and it also decrease the need for vasopressor therapy.Corticosteroids act by correcting a state of adrenal insufficiency, inhibiting synthesis of inducible nitric oxide synthase (INOS) leading to reduced production of nitric oxide and hence lesser vasodilatation, restoring the sensitivity of vascular catecholamine receptors and decreasing the transcription of inflammatory cytokines. Not only have steroids been shown to improve blood pressure but also administration of hydrocortisone during septic shock has been shown to reduce the Prevalence of post-traumatic stress disorder and improve the emotional well-being of survivors of septic shock the cortices study recommend that hydrocortisone should be considered in patients with fluid or vasopressor unresponsive patients

REVIEW OF LITERATURES

Pizarro et al[27] reviewed diagnostic criteria in children with severe sepsis and septic shock and treatment of adrenal insufficiency .According to him there was a various range of prevalence of adrenal insufficiency ranging from 15% to 61%. In critically ill patient, there were no established or accepted criteria to define adrenal insufficiency. To identify the adrenocortical hypo responsiveness, the rapid corticotropin stimulation test were used,. though there were controversy regarding the dose for stimulation test .He concluded that in children with severe sepsis and septic shock, adrenal insufficiency was common and adrenal insufficiency may be a contributing factor for the development for catecholamine –refractory shock but he was not able to substantiate the efficacy of low dose steroids as replacement therapy in severe sepsis and septic shock.

In a similar review article by casartelli et al[28], about adrenal insufficiency in children with septic shock, Though there were not any consensus to diagnose adrenal insufficiency in children with septic shock the condition that may suggest adrenal insufficiency

were volume refractory and catecholamine resistant septic shock and diagnostic criteria for adrenal insufficiency was a basal cortisol level < 25md /dl .He concluded that there was enough data to substantiate early replacement of low dose steroids in septic shock

Hana I et al[21] conducted a study in paediatric intensive care unit, in children's hospital, Cairo University. They studied the outcome of critically ill children who were admitted with sepsis and its relation with the adrenal state. The study was a case control in which about thirty case and thirty control were enrolled. They estimated baseline cortisol level and after high dose short ACTH stimulation test. Basal cortisol level of <7µg/dl and peak level after stimulation <18µg/dl was considered as absolute adrenal insufficiency. If cortisol raise after stimulation was <9µg/dl, it was considered as relative adrenal insufficiency. They concluded that in severe sepsis and septic shock, relative adrenal insufficiency was common and it was often associated with more inotropic support and higher mortality

Hatherill et al[29] conducted a study in children with septic shock to study the incidence of adrenal insufficiency, and its effect

on duration of intensive care , need for catecholamine support and mortality. He enrolled thirty three children with septic shock and assessed using short synacthen test and an increment of < 200 nmol/l was considered as adrenal insufficiency. The incidence of adrenal insufficiency in children in study population was 52%and overall mortality was 33%.children with adrenal insufficiency required higher dose of vasopressors, and longer period of inotropic support. But regarding duration of ventilation and mortality there was not significant difference between children with adrenal insufficiency and children with adequate reserves. They concluded that in children with septic shock adrenal insufficiency was common and associated with longer duration of shock and increased vasopressor requirement.

Sam et al[7] conducted a prospective observational study to determine the cortisol level in ICU patients, study done in Chicago. They measured the serum cortisol level in early morning sample within 48 hrs of admission in the hospital. Based on the morning serum cortisol level four groups were defined .They noticed higher

incidence of mortality in group with higher cortisol level They concluded that in severe sepsis there was elevated level of cortisol.

Han YY et al [30] conducted an experimental and clinical study which was a retrospective cohort study. He enrolled about 91 children from Dec 1993 to Jan 2001 a 9 year study, and practised resuscitation measures in consistent with ACCM- PALS guidelines. They noticed a overall mortality rate of 29 percent. There was a successful shock correction in 26 percent of children when the resuscitation was started in a median time of 75 minutes from arrival. Non survivors required more inotropic support than the survivors. Finally they concluded that improved outcome can be achieved by early recognition and stepwise escalation of fluids and inotropes following the guideline.

Annane et al [31] in another study demonstrated adrenal insufficiency in children with severe sepsis and septic shock. The study was an inception cohort study. They concluded that basal cortisol of value less than 10 mcg/dl or delta cortisol of less than 9 mcg /dl indicate adrenal insufficiency and unlikely when stimulated cortisol level is 44 mcg/dl or greater.

Gurupreet et al[32] conducted a study in children admitted in PICU from Rothak, Haryana, regarding the clinical outcome and predictors of mortality with sepsis ,severe sepsis and septic shock. Hemodynamic and laboratory parameters in children aged 1 to 14 yrs. admitted in PICU were studied. They enrolled about 50 patient with septic shock. Out of 50 patient in their study they recorded about 58 percent mortality and 42 percentsurvived and the median age was 18 months .They concluded that no individual factor determined the mortality like duration of stay or delay in transfer to PICU

A Prospective, descriptive study was conducted by Menon K et al[33] where he studied the adrenal dysfunction in critically ill paediatric patients. He enrolled about thirteen patients from pediatric intensive care unit inclusion criteria he used was PRISM score of about >/=10 and defined hemodynamic instability as fluid requirement > 20ml /kg and/or the need of inotropes in a24 hr period then he measured the basal cortisol level and ACTH level and post ACTH stimulation cortisol level. In this study , basal level of cortisol ranged from 0.10 to 37.4 with mean of 12.2+/- 9.6 . In

four out of thirteen patients had basal cortisol of <7 mcg /dl and post ACTH stimulation level < 18mcg/dl. They concluded that in response to stress the increase in basal cortisol level is not adequate but have a good response to stimulation test and help to determine the consequences of these parameters

A study by Burry LD et al[34]reviewing all articles on the septic shock adrenal insufficiency , corticosteroids a computerized search of all data base within time period , concluded that low dose corticosteroid should be administered empirically to all patients with septic shock and it may be discontinued if adrenal insufficiency is not confirmed.

Sarthi et al[26] conducted an study using low dose stimulation test in children with septic shock to determine adrenal status. The study was a prospective cross sectional study conducted in pediatric intensive care unit in a tertiary care hospital in northern India. They estimated cortisol level for children admitted with fluid refractory septic shock at baseline and after low dose synacthen stimulation at 30 minutes and 60 minutes. There was a higher incidence of catecholamine refractory shock inchildren with

relative adrenal insufficiency than in children with septic shock with adequate reserves but there was no difference in mortality They concluded that in children with septic shock, relative adrenal insufficiency was common and associated with catecholamine refractory shock Valoor et al [35] conducted an open labelled randomized study in pediatric intensive care unit. He recruited 38 children with septic shock who were refractory to fluid therapy alone. He gave Intravenous Hydrocortisone to these children for 7 days 5mg/kg/day in four divided doses on day 1 and half the dose thereafter for 7 days and other set of children were given normal saline. They found that there was early reversal of shock in this patient treated with hydrocortisone, and decreased requirement for inotropes, though not statistically significant. In both the group mortality was similar.

Bendel et al[36] conducted an prospective study in which they measured free cortisol level in sepsis and septic shock ,in which blood sample were taken and serum cortisol measured using electrochemiluminescence immunoassay and for calculating free cortisol , coolens method was used. They concluded that essential

information were not provided by calculation of free cortisol level in patient with sepsis and septic shock

Annane et al[37] conducted a multicentric randomized double blinded placebo controlled trial. In that study hydrocortisone was given to a set of patients and placebo given to another set. They conclude that reversal of shock was quicker in patient treated with hydrocortisone but it did not improve the survival and they also noticed that there was higher incidence of super infection that is new sepsis was seen in patients treated with hydrocortisone.

In another study by J. Atkinson et al[38] which was an retrospective study, He concluded that there was no improved outcome seen in children treated with corticosteroids and also that there was greater incidence of organ failure , higher mortality , higher illness severity and they had greater requirement of inotropes.

De jong et al[39] in an retrospective study conducted in medical and surgical unit studied 218 patients with septic shock in 3 year time frame and he measured cortisol pre and post stimulation with synthetic ACTH. in his study he concluded that

,there was an inverse relation to disease severity and cortisol response to ACTH.

Bouachour G et al[22] in an prospective clinical investigation had an contradictory result. In his study he enrolled about 40 patients and assessed the adrenocortical function by daily measuring the cortisol and measuring after a stimulation test within 24 hr of onset of shock. In his study only one patient had absolute adrenal insufficiency. . He concluded that single cortisol determination is of no value in the selected population also in patients with high cortisol level; ACTH stimulation test did not predict the outcome or estimate the adrenal insufficiency

Marik.Epaul et al[6] took fifty nine adult patients with septic shock and concluded that adrenal insufficiency was common in septic shock and basal cortisol about <25 mcg/dl was a better discriminator of adrenal insufficiency than the stimulation test

AzareK[40] reported that low dose corticosteroids administered in divided doses or continuous infusion is beneficial than high dose corticosteroids in decreasing the duration of inotropes and mortality in septic shock. Dexamethasone can be

used instead of Hydrocortisone, for patients for whom stimulation test cannot be done immediately

Goodman et al[41] conducted a prospective study and measured the basal and post stimulation cortisol level on day1, day 2and on day 28 of hospitalisation. He recruited about 34 patients in his study. he defined cortisol level < 15 mcg /dl as adrenal insufficiency and about 8 patient had adrenal insufficiency. The patients who had value <15 mcg /dl had longer duration of ICU and hospital stay. According to the study ICU and hospital stay was longer in patients with higher deta% . Delta % is the proportional change between basal and post stimulation cotisol level value he concluded that there was wide range of cortisol response and noticed that on day 28 in survivors and non survivors ,there was a difference in cortisol response patterns.

In another study done by Ratnarat R et al [42] in a fluid or catecholamine resistant septic shock concluded that basal cortisol value was more useful than the stimulation test . in his study he recruited about 29 patients with septic shock, and he measured the basal and post stimulation cortisol level. They considered as

steroid responsive, if they were able to discontinue vasopressor agent in 48 hours. They concluded that that basal cortisol measurement was a better indicator of outcome than the stimulation test.

SUBJECTS AND METHODOLOGY

OBJECTIVE

This study was designed to identify the prevalence of adrenal insufficiency which is evidenced by decreased serum cortisol level in children with fluid refractory or catecholamine dependant septic shock

STUDY

The study design was a prospective observational study. 49 children fulfilling the inclusion criteria were enrolled in study. The study was conducted in emergency department and paediatric intensive care unit., Institute of social paediatrics , Stanley medical college . An ethical committee approval was obtained. An informed consent was obtained from the parents/legal guardian before submitting a child to investigations and treatment

INCLUSION CRITERIA:

Children with age group between 1 month to 12yrs admitted with the diagnosis of septic shock or developed septic shock during the

stay in PICU, who were catecholamine dependent, were enrolled in the study.

EXCLUSION CRITERIA:

i. Child with inborn error of metabolism , primary adrenal insufficiency, with known hypothalamic pituitary dysfunction
ii. Child on immunosuppressant or chemotherapeutic agent.
iii. Children on steroid therapy or who received steroids in past 6 month.
iv. Children receiving phenytoin, phenobarbitone or rifampicin (Interferes with metabolism of catecholamine)
v. If parents have not given consent

CASE DEFINITION:

SIRS:

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

- Temperature of >38.5°C or <36°C.
- Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs or painful stimuli

- Mean respiratory rate >2 SD above normal for age
- Leukocyte count elevated or depressed for age

(Not secondary to chemotherapy induced leukopenia)

Or >10% immature neutrophils

SEPSIS:

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

Septic shock:

Sepsis +Anyone of the following criteria as presented in PALS EDITION: 2009-2010.

- Altered level of consciousness
- Tachypnea, with/without increased work of breathing
- Tachycardia
- Bounding peripheral pulses
- Brisk or delayed capillary refill
- Warm flushed skin peripherally (warm shock) or

  Pale mottled skin with vasoconstriction(cold shock)
- Hypotension with a wide pulse pressure (warm shock) or

Hypotension with a narrow pulse pressure (cold shock) or Normotension

- Fever or hypothermia

FLUID REFRACTORY SHOCK:

We had defined the catecholamine dependent septic shock as whenever the children not responded to fluid boluses of 20ml/kg up to 5 times or developed signs of pulmonary congestion whichever is earlier. The number of fluid boluses was increased to 5 in our study to give maximum allowance for children with acute diarrheal disorder.

CATECHOLAMINE DEPENDENT SHOCK:

Those children who were not responded to the maximum fluid boluses or developed signs of pulmonary congestion were started on inotropes and considered as catecholamine dependent shock.

Patients were subjected to

- A detailed history, general physical examination and systemic examination findings at the time of diagnosis of septic shock was recorded

- For all cases CARDIOPULMONARY ASSESSMENT was done and physiological status recorded.
- All the details were recorded in the proforma
- Appropriate investigations, such as complete blood count, renal function tests, liver function tests, urine analysis, blood/sputum/urine culture sensitivity, imaging studies etc was recorded on the proforma
- Appropriate fluid resuscitation, antibiotics and inotropics and ventilatory support, was instituted as per PEMC guidelines.
- The duration and type of fluid resuscitation, the type, dose and duration of inotropic support and time for weaning off inotropic support and antibiotics used was recorded on the proforma Specimen collection:
- Children with septic shock who were resistant to fluid therapy and when inotropes were started about 2 ml blood was drawn for estimation of serum cortisol.
- No time frame was considered as there is loss of diurnal variation in serum cortisol level in critically ill children.

- Blood sample was centrifuged and sent for investigation to the laboratory
- Serum cortisol was analysed and measured using ECLIA technique
- Adrenal in sufficiency was considered if random serum cortisol level was <18 mcg/ dl(496nmol/lt)

STATISTICAL METHODS

Data were collected and entered into Excel master chart. The collected data were analysed using statistical software SPSS 16 Package for Social Sciences (Version 16.0 (2007): SPSS Inc. Chicago, IL.). The parametric data were analysed by unpaired student's t-test and non-parametric data were analysed by Chi square test. The data (days of inotropic, ventilator support, PICU stay) were expressed as median with 95% confidence interval. Sample size of 49 was calculated usingOpenEPI, VERSION 2, open source calculator-SS proper to detect 30% prevalence of adrenal insufficiency.

5. RESULT

5.1 DEMOGRAPHIC DATA

5.1.1 AGE DISTRIBUTION :

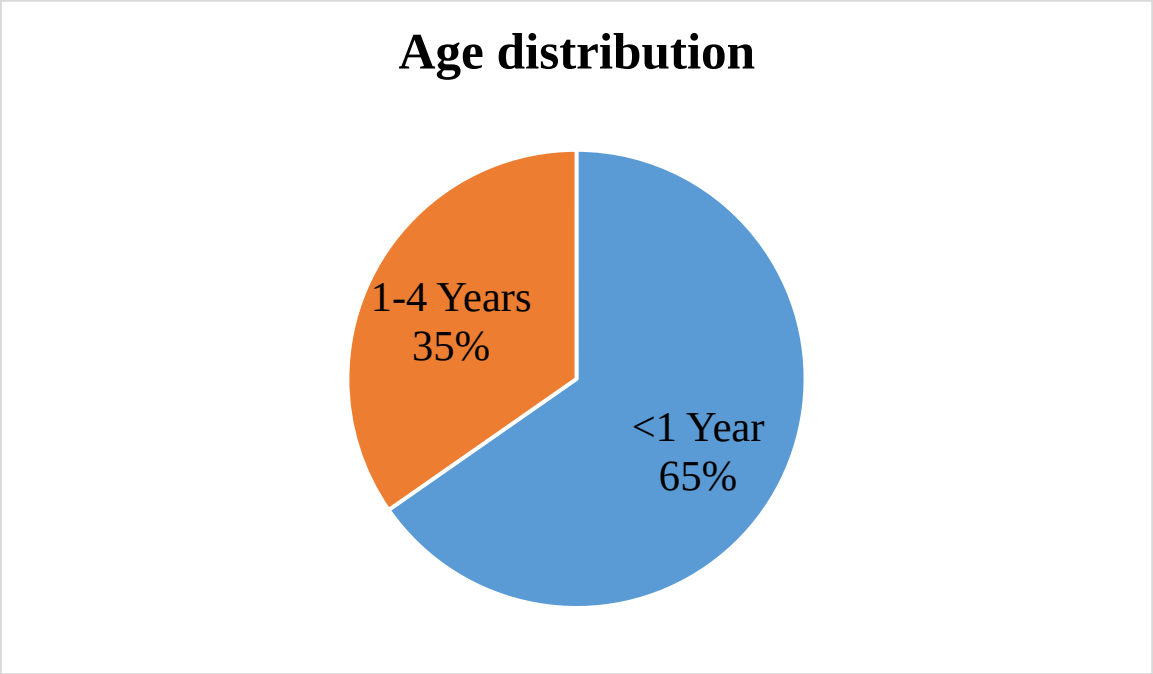

Figure 1: AGE distribution depicted as number and percentage of the total.

5.1.2 SEX RATIO

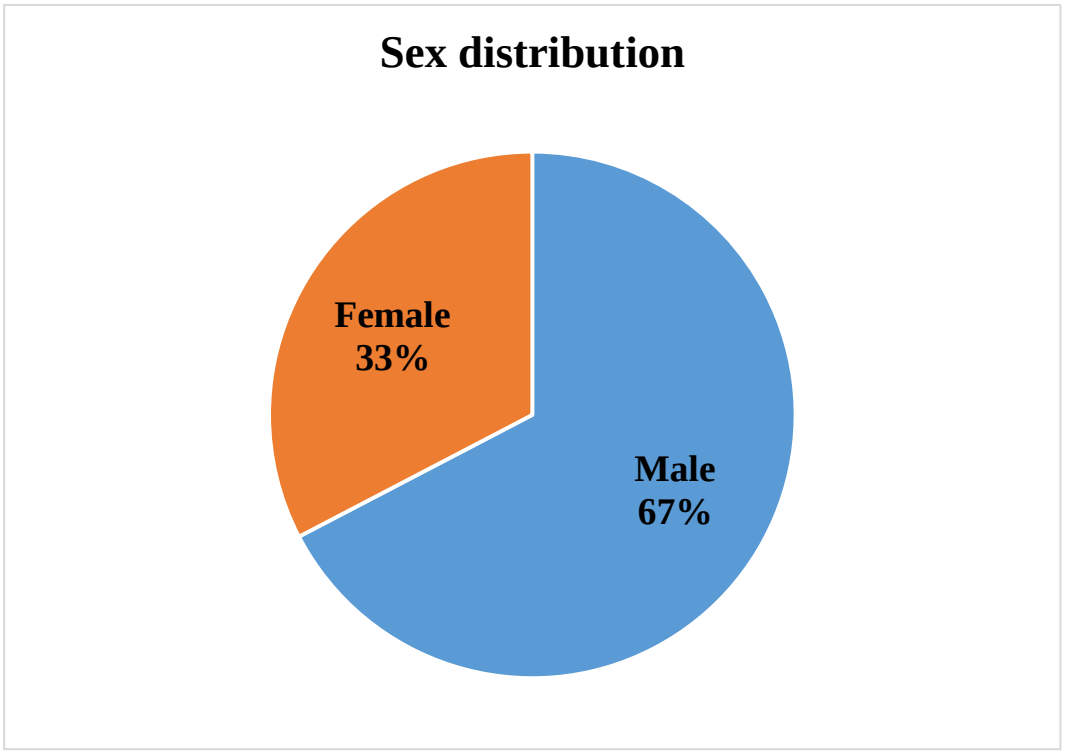

Figure 2: The sex distribution is depicted as number of children in each sex and percentage of total.

5.1.3 Diagnosis at PICU

Diagnosis	Low cortisol N=20	Normal cortisol N=29	Significance (P)
Broncho-pneumonia	13	21	
Bronchiolitis	3	2	
Late onset sepsis	2	2	**0.421**
Acute CNS infection	2	1	
Acute diarrhoeal disease	0	3	

Table 1: This table depicts the Diagnosis distribution among all the children in both the groups

5.2 PRIMARY OUTCOME MEASURE

5.2.1 SERUM CORTISOL LEVEL

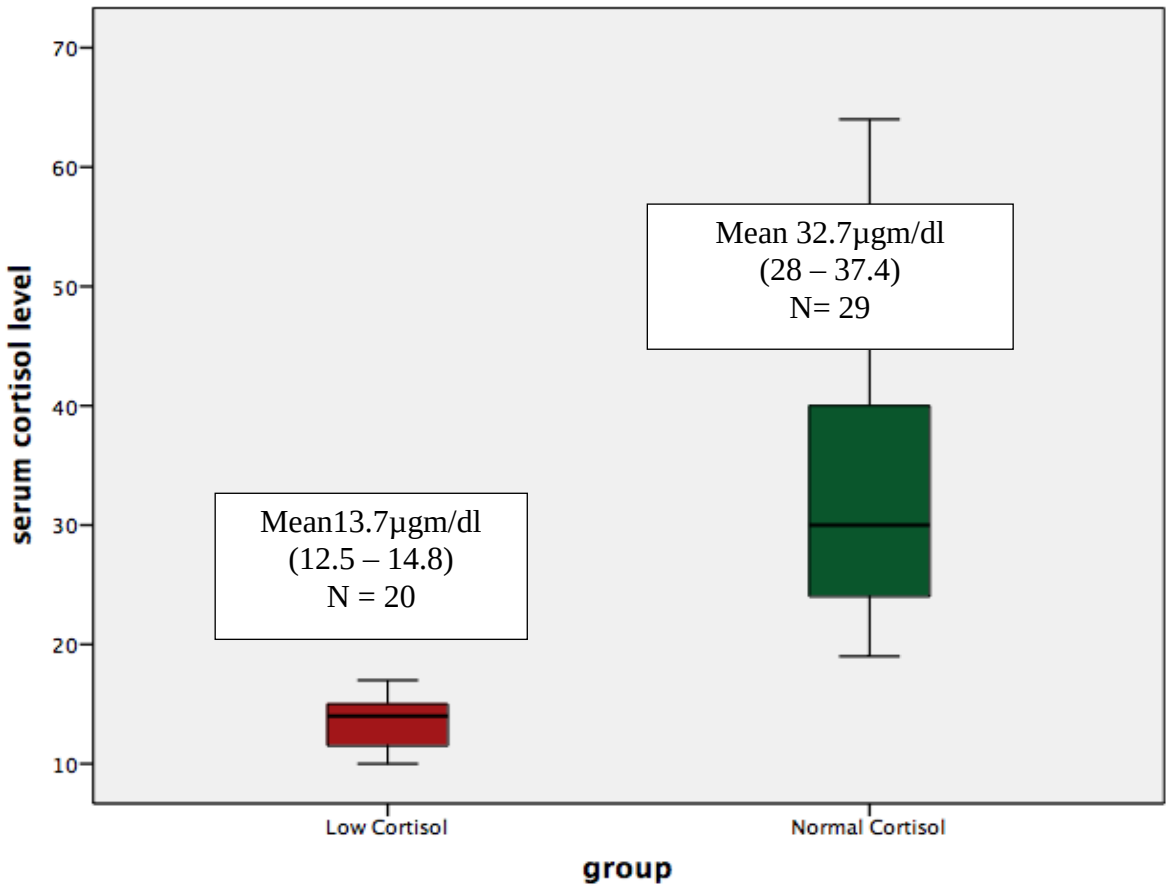

Figure 3: This graph depicts the serum cortisol (mean with 95% CI) in two groups LOW (less than 18 µgm/dl) and NORMAL (more than18 µgm/dl).

5.3SECONDARY OUTCOME MEASURE

5.3.1 Number of fluid boluses

No of fluid bolus20ml/kg	Low cortisol N=20	Normal cortisol N=29	SIGNIFICANCE (P)
1	4	0	0.621
2	11	13	
3	5	5	
5	0	1	

Table 2: This table depicts the number of fluid boluses administered in each group before deciding Inotropic support.

5.3.2 Number of inotropes required

No of inotropes required	Low cortisol N=20	Normal cortisol N=29	Significance(P)
1	15	22	0.602
2	5	7	

Table 3: This table depicts the number of inotropes required in each group of children

5.3.3 Duration of inotropic support (Days)

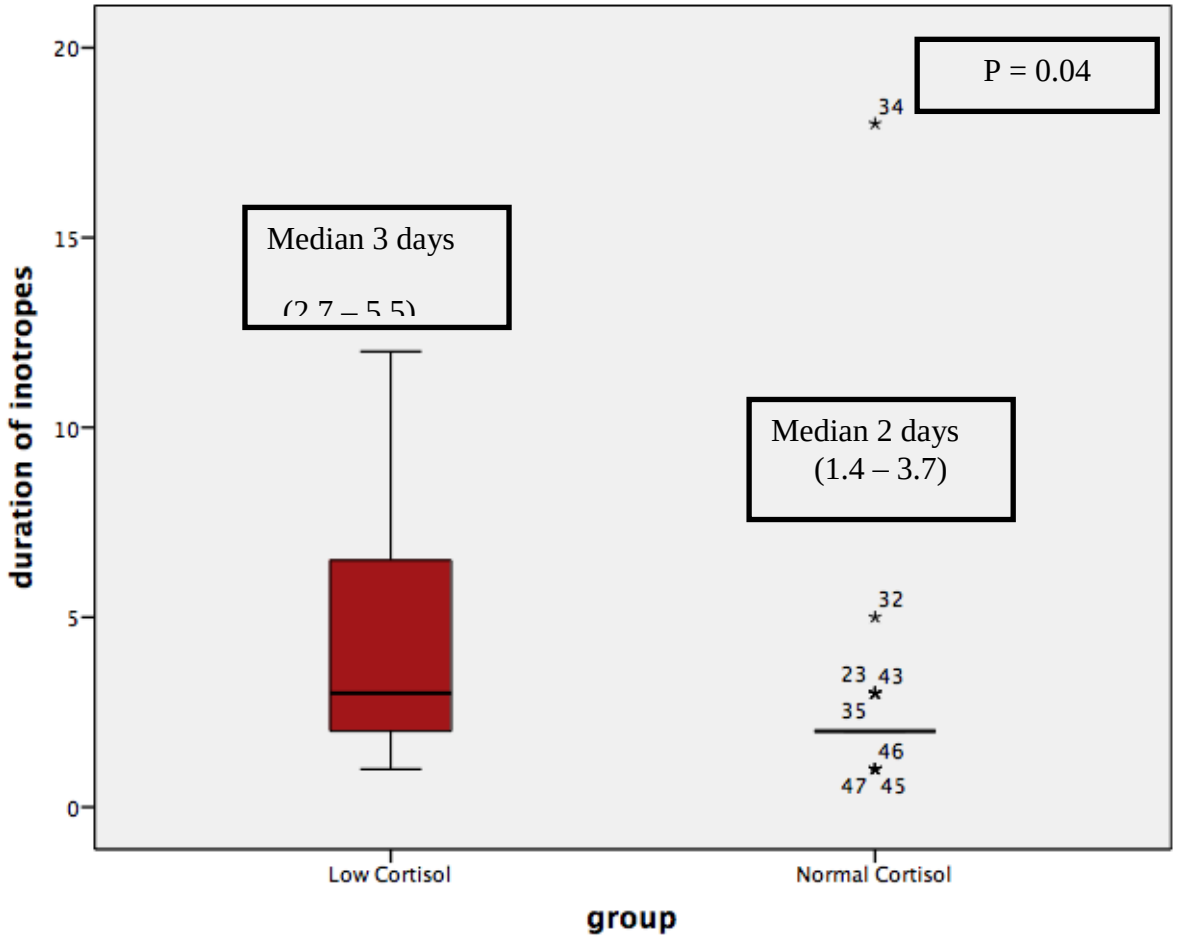

Figure- 4 This graph depicts the median days of inotropic support (95% CI) required in each group.

5.3.4 Duration of ventilator days

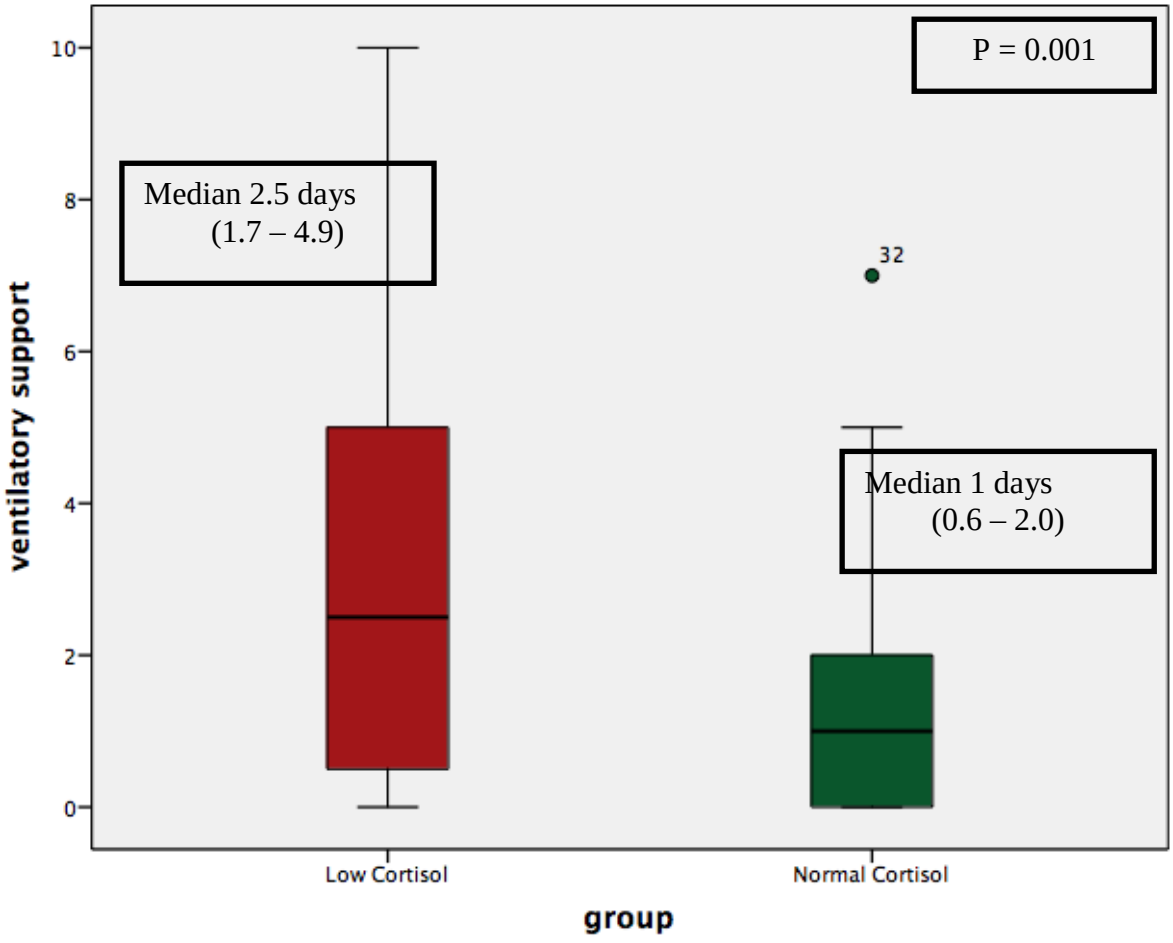

Figure 5 This graph depicts the median days of ventilatory support (95% CI) required in each group.

5.3.5 Duration of PICU stays (Days)

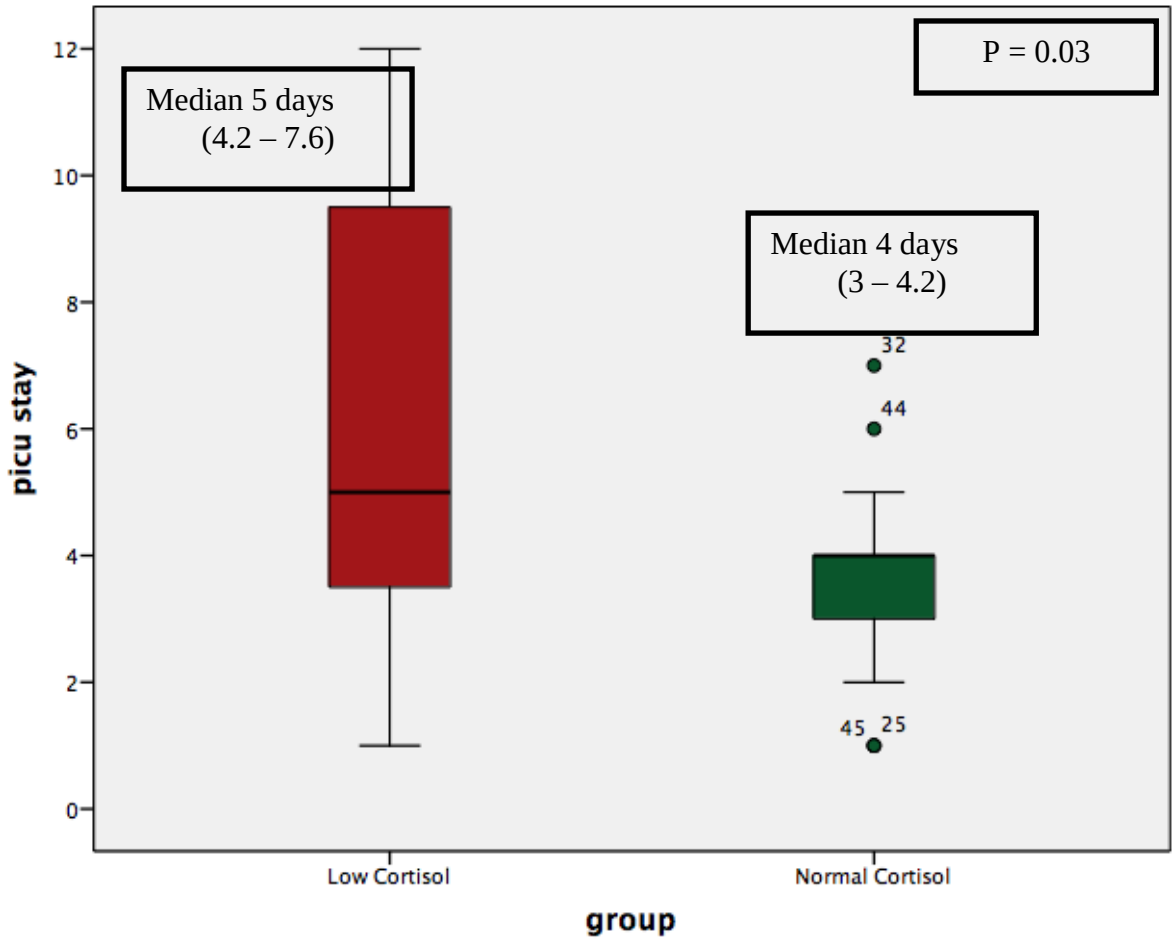

Figure 6 This graph depicts the median days of PICU stay (95% CI) in each group.

5.3.6 Duration of hospital stay (Days)

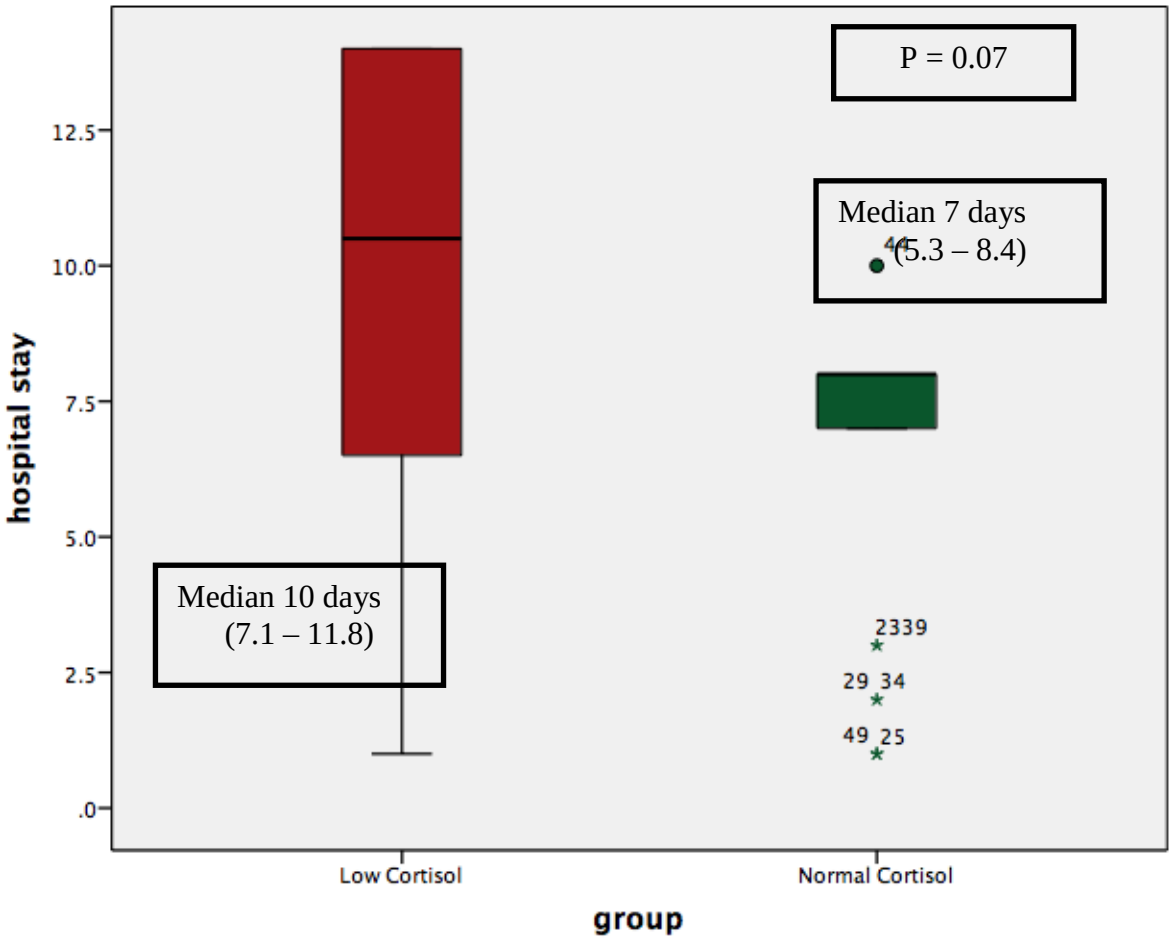

Figure 7 This graph depicts the median days of hospital stay (95% CI) in each group.

4.3.7 Treatment outcome

Treatment outcome	group		Significance (P)
	Low Cortisol N=20	Normal Cortisol N=29	
Expired	7	7	0.304
Survived	13	22	

Table 4: This table depicts the treatment outcome of all the children in both the groups.

DISCUSSION

This study was conducted in the department of social pediatrics, Stanley medical college, Chennai, during the period between September 2015 to August 2016. The institution's ethical committee approved this project (Annexure1). After getting informed consent from the parents 49 children fulfilling the inclusion criteria were recruited for the study by continuous sampling method. Children were managed as per standardized institute protocol. Blood sample was collected for serum cortisol when the child's hemodynamics did not respond to fluid boluses (fluid refractory shock) and required inotropic / vasopressor support. Random serum cortisol level was analyzed by ECLIA method. The ICU team was blinded to the serum cortisol levels and the subsequent management was not influenced by the results. Various study parameters like number of fluid boluses, type of inotropic support, duration of support, ventilator support, ICU stay, hospital stay and final treatment outcome were recorded. On analysis children were grouped in to **LOW or NORMAL serum cortisol group** depending on whether the serum cortisol level is

below or above 18 microgram per deciliter respectively. Their in hospital progress analyzed and compared against their serum cortisol level. At the outset the incidence of Relative Adrenal Insufficiency (Random serum cortisol level < 18 μgm/dl) in our study group was 41% (20) and these children required significantly longer duration of inotropic, ventilator support, PICU stay and hospital stay when compared to children having normal cortisol levels. The final treatment outcome in terms of in hospital mortality rate was comparable.

Demographic characteristics of study population

In our study group all children belonged to the age group less than 5 years among which 65 % were less than one year and 67% were male children. On analyzing the cause of septic shock, we found that bronchopneumonia contributes to two third of the diagnosis followed by bronchiolitis, late onset sepsis, acute CNS infection and Diarrheal disorder contributing to the remaining one third of the population in both the groups. Similarly Hanna et al [(21)] in their recent study demonstrated that the 63.3% of children suffering from pneumonia and 20% were suffering from diarrheal

disorder. In our study population late onset sepsis, acute CNS infection also contributed to the sepsis indicating the role of poor socio economic, nutritional and environmental factors on the incidence of various diagnoses.

Prevalence of Adrenal Insufficiency (AI)

We have defined the AI whenever the random serum cortisol level was below 18 μgm/dl (500nmol/l) which was the commonest value adopted by various authors [8,9,10,22,23] to define AI. The serum cortisol was measured by current standard electrochemiluminescence (ECLIA) method. In our study we have found that the prevalence of AI was 41% and the mean random serum cortisol level was 13.7 μgm/dl (95% CI; 12.5 - 14.8). The published prevalence of RAI is ranging from minimum of 2% to the maximum of 77% depending on the cutoff level used by the individual authors but considering our cut off point of 18 μgm/dl the prevalence was ranging from 30 to 60% [9,10,22] which was more in correlation with our observation.

AI and clinical outcome correlation

We had defined the catecholamine dependent septic shock as whenever the children did not respond to fluid boluses of 60ml/kg or developed signs of pulmonary congestion whichever is earlier. In our study we found that the duration of the hemodynamic and the respiratory support in terms of duration of inotropic support (Median of 3 vs 2 days; P= 0.04), ventilator days (Median of 2.5 vs 1 day; P = 0.001) and proportionately the PICU stays (Median of 5 vs 4 days; P = 0.03) were significantly prolonged in the children suffering AI when compared to children with normal cortisol level. Similarly, Menon k et al[33] also showed in his study that there was an increased duration of requirement of inotropes in children with adrenal insufficiency .whereas the total duration of hospital stay (Median days of 10 vs 7; P=0.07) and the mortality (7 children in each group 35% vs 24%; p=0.304) were comparable between the two groups. The results obtained in a similar study by Hatherill et al[29] .,also showed that there was no significant difference in mortality between children with adrenal insufficiency and those with normal reserves. The basal random serum cortisol level less

than 7 μgm/dl is considered to define absolute adrenal insufficiency. .

The role of glucocorticoid cortisol during stress response is well established. It is required for haemodynamic stability, metabolism and anti-inflammatory activity [24]. It maintains the vascular tone, cardiac contractility, and potentiates the action of catecholamine. Serum cortisol provides significant anabolic activity in terms of amino acid and lipid mobilization, increases gluconeogenesis and moderate reduction in the rate of glucose utilization. The anti-inflammatory effects are needed to decrease the capillary permeability, neutrophil and macrophage activation and modulate the cytokine release [25]. Hence in our study children with low serum cortisol required more prolonged inotropic support to maintain the hemodynamic similarly pulmonary capillary leak, attending congestion and hypoxemia requires prolonged ventilator support. Both hemodynamic and respiratory support prolongs the PICU stay of these children when compared to the children with normal serum cortisol. Similar observation was made by many authors [21, 26] On the contrary our mortality rate and overall

hospital stay was comparable between the two groups. This could be because of the virulence of the microorganism, bacterial or viral, and the amount of multi organ dysfunction at the time of PICU admission. Since we have not studied all these factors their influence on the mortality could not be commented. The discharge from the health care in our poor socio economic status was dependent on lot other factors like transport, availability of reliable attender more than a rigid protocol driven discharge criteria. Hence we were not able to rely on the hospital discharge as a marker of disease prognosis.

Limitations of the study

We analyzed one time random serum cortisol level to determine the adrenal function. The influence of circadian variation, stress test like low dose or high dose stimulation test had not been done to delineate the absolute or relative adrenal insufficiency. The other influencing factors of mortality like microorganism and its sensitivity, antibiotic therapy, co morbidities etc were not studied and included in the analysis.

Futuristic plan

To include stimulation test to identify the relative, absolute adrenal insufficiency and institute steroid supplementation (Intervention) in the form of blinded randomized controlled trial and study the influence on out come so that we can understand the role of adrenal function in the sepsis and contribution of supplementary therapy towards the better outcome.

Conclusions

In our study population with the present methodological design we found that the prevalence of adrenal insufficiency was common and mounts to 41%. Children associated with low serum cortisol needed prolonged inotropic and ventilatory support leading to more days of ICU care when compared to the children with normal cortisol levels. Still the overall mortality and hospital stay was comparable. Hence we concluded that the low serum cortisol was a common finding among children suffering catecholamine dependent septic shock and it was positively correlated with prolonged hemodynamic, respiratory support and ICU care. We required further study to delineate the incidence of absolute and relative adrenal insufficiency by doing a stimulation test and required controlled randomized trials to analyze the benefits of steroid supplementation on morbidity and mortality of these children.

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Abstract

Background: Adrenal glucocorticoid cortisol maintains the cardiovascular function, decreases the catabolism and stabilizes the alveolar capillary membrane during inflammatory stress period.

Aim : To determine the prevalence of adrenal insufficiency by measuring serum cortisol level in children with catecholamine dependent septic shock.

Method: 49 children admitted with catecholamine dependant septic shock satisfying inclusion criteria recruited in to the study. Random serum cortisol was measured and correlated with various prognostic parameters like duration of inotropic and ventilator support, PICU and hospital stay and mortality.

Result: The prevalence of adrenal insufficiency (< 18µgm/dl) was 41%. Duration of inotropic support (Median of 3 vs 2 days; P= 0.04), ventilator days (Median of 2.5 vs 1 day; P = 0.001) and proportionately the PICU stays (Median of 5 vs 4 days; P = 0.03) were significantly prolonged in the children with low cortisol when compared to children with normal cortisol level. Whereas the total

duration of hospital stay (Median days of 10 vs 7; P=0.07) and the mortality (7 children in each group 35% vs 24%; p=0.304) were comparable between the two groups.

Conclusion: we concluded that the low serum cortisol was a common finding among children suffering catecholamine dependent septic shock and it was positively correlated with prolonged hemodynamic, respiratory support and ICU care. We require further study to delineate the incidence of absolute and relative adrenal insufficiency by doing a stimulation test and also require controlled randomized trials to analyze the benefits of steroid supplementation on morbidity and mortality of these children.

APPENDIX

APPENDIX-I	**ETHICALCOMMITTEE CERTIFICATE**
APPENDIX-II	**INFORMATION SHEET**
APPENDIX-III	**CONSENT FORM**
APPENDIX-IV	**PERFORMA**
APPENDIX-V	**MASTER CHART**
APPENDIX-VI	**PLAGIRISM**

APPENDIX-I

ETHICAL COMMITTEE CERTIFICATE

INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Serum cortisol level in catecholamine dependent Septic shock in Children of Age group 1 month to 12 Years. .

Principal Investigator : Dr E Vijaya Bharathi.

Designation : PG MD (Paediatrics)

Department : Department of Paediatrics
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 29.09.2015 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

APPENDIX-II

INFORMATION SHEET FOR THOSE WHO PLAN TO PARTICIPATE IN THE RESEARCH PROJECT

NAME OF THE RESEARCH PROJECT:

Serum cortisol level in children with catecholamine dependant shock – A prospective observational study

We welcome you and thank you for having accepted our request to consider whether you can participate in our study. This sheet contains the details of the study; the possible risks, discomfort and benefits for the participants are also given.

You can read and understand by yourself; if you wish, we are ready to read and explain the same to you.

If you do not understand anything or if you want any more details, we are ready to provide the details.

Information to the participants:

What is the purpose of the study?

To know the levels Serum cortisol level in catecholamine dependent septic shock.

Who / where this study is being conducted?

PICU, I nst of social pediatrics, stanley medical college,

Why I am being considered as one of the participant?

Because, you are one of the person who satisfying all our inclusion and exclusion criteria of our study

Should I definitely have to take part in this study?

No. If you do not wish to participate, you will not be included in this study. In addition, you will continue to get the medical treatment without any prejudice.

If I am participating in this study, what are my responsibilities?

Your responsibilities are

i. To allow us to perform blood investigations(2 ml of blood will be drawn)
ii. To co-operate while performing the test
iii. To answer reliably when asked for
iv. To inform if you have any discomfort during the study period

Are there any benefits for me / public?

Yes.

Will there be any discomfort / risks to me?

There is no risk involved in this study. Mild discomfort

Will I be paid for the study?

No. You will not be paid.

Will my participating in this study, my personal details will be kept confidentially?

Yes, confidentiality will be maintained.

Will I be informed of this study's results and findings?

Yes, if you want you can get the details from us.

Can I withdraw from this study at any time during the study period?

Yes. You can withdraw at any time during the study period.

APPENDIX-III

CONSENT FORM

I _____ have been informed about the details of the study in own language.

I have understood the details about the study.

I know the possible risks and benefits for me/Son /dauguter, by taking part in the study.

I understand that we can withdraw from the study at any point of time and even then, I will continue to get the medical treatment as usual.

I understand that I will not get any payment for taking part in this study.

I will not object if the results of this study are getting published in any medical journals, provided my personal identity is not reviewed.

I know what I am supposed to do by taking part in this study and I assure that I will give my full co-operation for this study.

I nominate ----------(name) (mention the relation) to be my dependant to receive compensation if any.

Signature/Thumb impression of the participant

(Name/Address/Occupation/Monthly income)

_____

_____

_____

Signature/Thumb impression of the witness (Name/Address)

_____

_____

_____

Name & Signature of the investigator

_____

APPENDIX-IV

DATA COLLECTION PROFORMA

Name: Age:

Op/Ip no: Sex:

Address:

DOA: DOD:

Presenting complaints:

1. fever
2. cough/rapid breathing/chest retractions:
3. vomiting/blurred vision/headache:
4. diarrhea/vomiting:
5. rash/joint pains/bleeds:
6. hematuria/facial puffiness
7. others/co-morbidities(ear discharges convulsions

Dysuriaincreased frequency of urine)

General physical examination:

Pallor/icterus/Cyanosis/clubbing/ lymphadenopathy/oedema

Weight:

Central pulses/ peripheral pulses (bounding/feeble):

Peripheries (warm/cold):

Capillary refilling time:

Urine output:

Vital sign:

Heart rate/pulse rate:

Respiratory rate:

Temperature:

BP(normal/low):

Cold shock/warm shock

(Compensated/uncompensated septic shock)

Cardiopulmonary assessment will be done

Systemic examination:

CVS

RS

PER ABDOMEN

CNS

INVESTIGATIONS:

1. Complete hemogram- Hb

TLC/DLC

PCV

Platelets

2. RENAL FUNCTION TEST -RBS

-blood urea

-Sr. creatinine

3. Serum Electrolytes

4. CRP

4 .ESR

6. CHEST X-RAY

7 .Blood c/s

8 .Sr .Cortisol

9 Imaging studies

TREATMENT GIVEN:

Antibiotics- 1st line

2nd line

3rd line

Inotropes (dose duration and time for weaning)

Dopamine

Dobutamine

Noradrenaline

Fluid for resuscitation:

Volume of fluid

Type of fluid: Crystalloid-NS/RL

Colloids- albumin/blood

OUTCOME:

1. Recovery / death.

2. Duration of inotropes

3. Duration of ventilator support

4. Duration of stay in hospital stay.

APPENDIX -V

MASTER CHART

	name	age	sex	no of bolus	no of inotropes	duration of inotropes	ventilatory support	blood transfusion	picu stay	hospital stay	outcome	diagnosis	serum cortisol level
2	swetha	1.3yrs			3	1	2		2	3	7 IMPROVED	Bronchopneumonia	25.39
3	b/o jeeva	36/365	F		3	1	4	5	2	7	11 IMPROVED	Bronchiolitis	26.73
4	manushka	9 mon	F		2	1	3		2	5	8 IMPROVED	bronchopnumnia	20.82
5	sanjana	9 mon	F		2	1	1		2	3	7 IMPROVED	bronchopneumonia	54.09
6	rosika	9 mon	F		2	1	1		2	4	8 IMPROVED	bronchopneumonia	46.73
7	vetrivel	7 mon	M		2	1	2		2	4	10 IMPROVED	bronchopneumonia	28.54
8	dhivyasri	10mon	F		2	1	1		2	3	7 IMPROVED	bronchopnemonia	36.76
9	vishal	9 mon	M		1	1	2		2	5	8 IMPROVED	bronchoitis	40.08
10	pragathi	7 mon	F		1	1	3	3	2	5	10 IMPROVED	bronopneumonia	26.34
11	ismail	1.5 yrs	M		3	1	2		2	4	7 IMPROVED	bronchopneumonia	26.23
12	veera	3 mon	M		1	1	2		2	6	12 IMPROVED	Late onset sepsis	25.56
13	sooraiya	34/365	F		1	1	2	2	2	4	14 IMPROVED	Bronchiolitis	28.54
14	shashanth	2yrs	M		3	1	3		2	7	14 IMPROVED	Bronchopneumonia	27.63
15	abdul kalam	2mon	M		2	2.7 hrs	7hrs		1.7 hrs	7 hrs	EXPIRED	Late onset sepsis/refractory shock	13.52
16	harish	2 mon	M		2	1	2	5	2	12	14 EXPIRED	Bronchopneumonia	15.08
17	joshika	1.5yrs	F		3	2	3	3	2	3	3 IMPROVED	acute CNS infection	20.83
18	sricharan	9 mon	M		1	1	2		2	4	8 IMPROVED	Bronchiolitis	34.82
19	shifra	1yrs	F		3	1	2	2	2	4	8 IMPROVED	bronchopneumonia	23.34
20	sanjay	1yrs	M		1	1.1hr	1 hr		2.1 hr		1 EXPIRED	bronchopneumonia	25.56
21	mohammad jaleel	6 mon	M		1	1	2	1.5	2	3	8 IMPROVED	bronchopneumonia	31.33
22	miyama	1.3yrs	F		2	1	2		2	4	8 IMPROVED	ADD/septic shock	63.44
23	aliya	3yrs	F		3	1	3	3	2	5	10 IMPROVED	Bronchiolitis	27.54
24	lokesh	1yrs	M		3	2	5	7	1	7	7 EXPIRED	bronchopneumonia	25.43
25	sundar	8 mon	M		1	2	1	1	2	1	1 EXPIRED	bronchopneumonia	22.45
26	santhosh	9 mon	M		2	1	2	2	2	4	8 IMPROVED	bronchopneumonia	21.22
27	dharshan	3 mon	M		2	1	9	10	2	12	14 IMPROVED	bronchopneumonia	23.45
28	lekha	2yrs	F		2	1	2		2	4	8 IMPROVED	bronchopumonia	22.73

28	lekha	2yrs	F	2	1	2			2	4	8 IMPROVED	bronchopnumonia		22.73
29	jeevitha	1yrs	F	2	1	2			2	3	7 IMPROVED	bronchopneumonia		31.32
30	b/o bhavani	48/365	M	1	2	2	3		2	3	3 EXPIRED	late onset sepsis		31.34
31	thushyanthini	2 moon	F	2	1	3	5		2	9	14 IMPROVED	bronchopneumonia		28.53
32	parameshwari	1yrs	F	2	2	1	1		2	1	1 EXPIRED	acute CNS infection		10.08
33	harish	1yrs	M	2	1	3			2	5	8 IMPROVED	bronchopneumonia		41.23
34	mohamad harafad	5 moon	M	1	2 12 hrs	12hrs			2 12 hrs	12 hrs	EXPIRED	bronhopneumonia		11.44
35	divya	3yrs	F	3	2	6	10		2	10	10 EXPIRED	rt upper lobe pneumonia		23.25
36	sabarinasan	2moon	M	1	1	3	5		2	6	10 IMPROVED	bronchopneumonia		41.32
37	ethvin	8 moon	M	2	1	8	7		2	11	14 IMPROVED	bronchopneumonia		23.64
38	kamesh	2 moon	M	2	1	3	4		2	5	8 IMPROVED	bronchopneumonia		29.53
39	rajashree	3 moon	F	2	1	4	5		1	5	5 EXPIRED	bronchopneumonia		17.32
40	sai	5 moon	M	2	2	1.5	1.5		2	1.5	1.5 EXPIRED	bronchopneumonia / MODS		24.32
41	akash	3 moon	M	2	1	7	8		2	10	14 IMPROVED	Bronchopneumonia		27.63
42	joshwa	10 moon	M	2	2	1	1		2	1	1 EXPIRED	ADD/septic shock		13.63
43	b/o saveetha	44/365	M	1	1	2	3		2	4	8 IMPROVED	late onset sepsis		19.34
44	dinesh	5 moon	M	2	2	1	1		1	1	1 EXPIRED	bronchopneumonia/ref septic shock		10.46
45	b/o ponni	4 moon	M	1	1	2			2	3	8 IMPROVED	bronchopneumonia		31.33
46	radhika	1yrs	F	3	1	2			2	3	8 IMPROVED	bronchopneumonia		23.93
47	sai sastha	10 moon	M	1	1	2	3		2	4	8 IMPROVED	bronchopneumonia		24.78
48	Rhea	3 moon	F	5	2 18hrs	18hrs			2 18Hrs	18HRS	EXPIRED	ADD/septic shock		28.76
49	Rohith	1.6yrs	M	2	1	2			2	4	8 IMPROVED	bronchopneumonia		23.56
50	Mohd.Faizal	4yrs	M	2	1	2			2	5	12 IMPROVED	acute CNS infection		34.93

APPENDIX -VI

PLAGIARISM CERTIFICATE