"SERUM LACTATE AS A PROGNOSTIC MARKER IN PATIENTS WITH SEPSIS-A PROSPECTIVE STUDY"

By

DR. SUHAS T

Dissertation submitted to

In partial fulfillment for the degree of

MASTER OF SURGERY

IN

GENERAL SURGERY

Under the guidance of

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VIJAYAPUR – 586103

2017

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"SERUM LACTATE AS A PROGNOSTIC MARKER IN PATIENTS WITH SEPSIS- A PROSPECTIVE STUDY"**is a bonafide and genuine research work carried out by me under the guidance of **DR. RAMAKANTH BALOORKAR,** Associate Professor, Department of General Surgery, Shri. B.M. Patil Medical College, Hospital and Research centre, Vijayapur.

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ACKNOWLEDGEMENT

On completion of my post graduation journey and this scientific document, I would like to acknowledge the immense help received from my mentors in the Department of General Surgery.

*With privilege and respect I would like to express my gratitude and indebtedness to my Guide,**Dr. RamakanthBaloorkar,**for hisconstant inspiration, extensive encouragement and loving support, which he rendered in pursuit of my post-graduate studies and in preparing this dissertation.*

*I am forever grateful to Professors,**DrTejaswiniVallabha,DrM.B.Patil, Dr.AravindPatil, Dr.B.B.Metan,Dr.M.S.KottenavarDr.VijayaPatil**for their guidance and encouragement provided to me, to achieve new heights professionally over my course period.*

I am grateful to AssociateProf.Dr.Basavaraj.Narasangi, Dr.Hemanth.Kumar, Dr.Girish .Kulloli for their guidance, encouragement and inspiration.

I am thankful to Dr. Dayanand..S.Biradar, Dr.Vikram.Sindagikar, Dr.Deepak.Chavan, Dr.S.S.Patil, Dr.Shailesh.Kannur, Dr.Surekha.Rathod,Dr. Harshavardhan.Biradarfor their great help.

I am extremely thankful to Prof. Dr.S P Guggarigoudar, Principal, of B.L.D.E.U'S Shri.B.M. Patil Medical College, Hospital and Research Centre, VIJAYAPUR, for permitting me to utilize resources in completion of my work.

I also thank MrMohd. ShahnawazLecturerStatistics, for his guidance during my dissertation work.

My thanks to one and all staff of Library, GENERAL SURGERY Department and Hospital for their co-operation in my study.

I am thankful to my seniors,Dr.Ashrith.I.M, Dr.Sunil.K, Dr.Rakshith, Dr.Bharath, Dr.Ravi.I, Dr.Anikethan.V, Dr.Anand.S, Dr.Jadesh, Dr.Umesh, Dr.Rohith, Dr.Mallikarjun, Dr.Abhilashfor their advice, suggestions and co-operation in my journey.

I would also like to thank my colleaguesDr.KeeniDilipReddy,Dr.AhmedFaraz Patel, Dr.Anup.Kubsad,Dr. Varun Kumar Damera, Dr.MrinalKumar,Dr.Krutifor their help and co-operation.

I would also like to thank my juniors Dr.Balakrishna, Dr.Vijaykumar, Dr.Surya, Dr.Santhosh, Dr. Manoj, Dr.Harsh,Dr. Ritesh for their support and co-operation.

I am deeply indebted to my parents A.S.THOTAPPA SHETTY & SHOBHA K S for their blessings,and my brother Dr.Ullas T which helped me to complete this dissertation.

My heartfelt thanks to my wife DrChaitra.M.V for her help, constant encouragement and moral support that led me to successfully complete this dissertation work.

Last but not the least; I convey my heartfelt gratitude to all my patients, without whose co-operation, this study would be incomplete.

DR. SUHAS T

ABSTRACT

Background & Objectives:

This was a prospective study to estimate the Serum Lactate levels and as a prognostic marker in patients with Sepsis. To estimate the serum lactate values at the time of admission and the second sample value at 24-48 hrs after admission and to predict the outcome of patients with sepsis based on serum lactate levels and its clearance.

Methods:

This study consists of 170 selected cases patients admitted with sepsis condition in B.L.D.E.U s Shri. B. M.Patil Medical College, Hospital and Research Centre, Vijayapur from October 2014 to June 2016.

Results:

In thisstudy the mean serum lactate value of first sample in survivors (146 patients) is 3.8 ± 1.2 and nonsurvivors(24 patients) is 6.2 ±1.9 with p value <0.001 which is significant. The serum lactate value of the second sample in survivors(146) is 2.7 ±1.0 and in nonsurvivors(24) is 6.3±1.8 with p value <0.001 which is significant.The mean value of serum lactate 1st sample collected at the time of admission is 4.1±1.6 and the mean value of serum lactate second sample collected at 24-48 hrs after admission is 3.1±1.6.Highly significant difference is there between serum lactate 1st and 2nd sample with p value <0.001 which is significant.Hence serum lactate is considered as a prognostic marker in patients with sepsis and evaluates the treatment outcome.

Interpretation and Conclusion:

Fall in lactate concentration following the initiation of treatment for sepsis is due to an attenuation of the stress response. Lactate levels are one of the most used biomarkers in sepsis. When their level is more than 4 mmol/L patients are at highest risk of mortality and an aggressive resuscitation strategy shall be warranted.This study suggests an important role for serial sampling of the subsequent two lactate values and lactate clearance as a prognostic indicator of sepsis.Patients with initial serum lactate value >4.0 mmol/L were independently associated with mortalityand serum lactate had a positive correlation with outcome of sepsis.Hence serum lactate is considered as a independent and significant prognostic marker in patients with sepsis and evaluates the treatment outcome.

Keywords: Sepsis, Serum lactate, prognostic marker

ABBREVIATIONS

PR	-	PULSE RATE
RR	-	RESPIRATORY RATE
SBP	-	SYSTOLIC BLOOD PRESSURE
DBP	-	DIASTOLIC BLOOD PRESSURE
TEMP	-	TEMPERATURE
RBS	-	RANDOM BLOOD SUGAR
B.UREA	-	BLOOD UREA
S.CREATININE	-	SERUM CREATININE
Yrs	-	Years
LPS	-	Lipopolysaccharide
C5	-	Compliment factor 5
COX-2	-	Cyclooxygenase 2
PGE2	-	Prostaglandin E2
CD	-	Cluster of differentiation
DNA	-	Deoxyribo nucleic acid
TIR	-	Tol like receptor
IL	-	Interleukin
TNF	-	Tumor necrosing factor
TF	-	Tissue factor
aPC	-	Activated protein C
MAL	-	Myeloid differentiation 88 adaptor like
MD	-	Myeloid differentiation
LBP	-	Lipopolysaccharide binding protein

TIR	-	toll/interleukin1 receptor homology domain
IRAK	-	Interleukin1 receptor associated kinase
PKR	-	RNA dependent protein kinase
IRF	-	Interferon regulatory factor
NOD	-	Nucleotide binding oligomerisation domain
APaf	–	Apoptotic protease activating factor
MOF	-	Multi organ failure
MAC	-	Major histocompatibility complex
ARDS	-	Acute respiratory distress syndrome
TREM	-	Triggering receptors expressed on myeloid cells
PEEP	-	Positive end expiratory pressure
Pao2	-	Partial pressure of oxygen
Fio2	-	Fractionated inspired oxygen
HIV	-	Human immunodeficiency virus
PDH	-	Pyruvate dehydrogenase
Acetyl- CoA-		acetyl coenzyme A

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INTRODUCTION

Sepsis is a clinical syndrome characterised by systemic inflammation due to infection. There is a continuum of severity ranging from sepsis to septic shock.

Sepsis is a complication of infectious process that is characterised by systemic inflammation with widespread tissue injury. Even with optimal treatment,mortality due to severe sepsis or septic shock is approximately 40 percent and can exceed 50 percent in the sickest patients.[1]

Septic shock is a extreme clinical condition involving tissue hypoperfusion where tissue oxygen demand can exceed the ability of tissues to extract oxygen from the limited oxygen supply. Sepsis additionally impairs the ability of tissues to extract oxygen so that ATP generation from glucose oxidation is supplemented by ATP generation from glycolysis leading to lactate production.[2]

Lactate is a product of anaerobic glucose metabolism. It is generated from pyruvate with lactate dehydrogenase as a catalyst.Lactate is cleared from blood, primarily by the liver, with the kidneys and skeletal muscles to a lesser degree. Cardiopulmonary failure, sepsis, trauma, oncologic pathology etc can lead to lactic acidosis.

Hepatic and muscle clearance of lactate may also be impaired thus blood lactate concentration are often elevated in sepsis.Rather than thinking of lactate solely as a byproduct of inadequate blood perfusion it may be useful to consider lactate as a marker of strained cellular metabolism. [2]

The primary goal in management of sepsis is to restore adequate oxygen and substrate delivery to the tissues as quickly as possible and to improve the tissue oxygen utilization and cellular metabolism.Serum Lactatewas chosen because it is used as a prognostic marker of globalhypoxia and the clearance of circulating lactateis

prolonged inpatients with sepsis. Samples of venous blood for lactate can be used asthese samples are easily obtained and the results are roughlyequivalent to those of assays of arterial samples.[3]

Hence as a measure of tissue hypoxia and risk stratification lactate measurement have now been incorporated in to treatment protocols of sepsis.[4]

Henceforth this study is being done to assess the role of serum lactate as a predictor of outcome in patients with sepsis.

AIMSAND OBJECTIVES OF THE STUDY

- To estimate the Serum Lactate levels and as a prognostic marker in patients with Sepsis.
- To predict the outcome of patients with sepsis based on serum lactate levels.

REVIEW OF LITERATURE

DEFINITIONS:

INFECTION:

Microbial phenomenon characterised by an inflammatory response to the presence of micro organisms or the invasion of normally sterile host tissue by those organisms.

BACTEREIMIA: The presence of viable bacteria in the blood.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME(SIRS):

The systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions:

1) Temperature>38^0 C or <36^0 C

2) Heart rate >90 bpm

3) Respiratory rate >20 breaths per minute or PaCO2 <32mm Hg

4) WBC count >12000 per mm^3 or <4000 per mm^3 or >10% immature (band forms)

SEPSIS:

The systemic response to the infection manifested by two or more of the following conditions as a result of infections:

1) Temp>38^0 C or <$36\ ^0$ C

2) Heart rate >90 bpm

3)Respiratory rate >20 breaths per minute or Pa CO2 <32 mm Hg.

4) WBC count >12000 per cumm or <4000 per cumm, or >10% immature (band forms).

SEVERE SEPSIS:

Sepsis associated organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may includelactic acidosis, oliguria or an acute alteration in mental status.

SEPTIC SHOCK:

Sepsis induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include lactic acidosis,oliguriaor an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time perfusion abnormalities are measured.

SEPSIS INDUCED HYPOTENSION:

A systolic blood pressure <90 mm Hg or a reduction of >= 40mm Hg from baseline in the absence of other causes for hypotension.

MULTIPLE ORGAN DYSFUNCTION SYNDROME (MODS):

Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.[5]

PATHOPHYSIOLOGY OF SEPTIC SHOCK:

Survival requires the host firstto detect either tissue invasion or tissue damage andsecond to repel the invaders or to repair the damage. The autonomic nervous systemfunctions as a “sixth sense” to detect invasion of microbes or evidence of trauma, andserves as the surveillance system that sets the stress response in motion [7]. The autonomicnervous system treats trauma and infection as the same emergency [8] and canbe activated by a variety of stimuli. Hypotension, a consequence of reduced cardiacoutput in shock, has long been known to activate secretion of the classical stress hormones.

When activated, the autonomic nervous system produces arteriolar constriction, venouscapacitance vessel constriction, increased heart rate, and augmented contractility. It stimulates both the renin angiotensin system ,the secretion of epinephrine and other medullary adrenal hormones.

Renin enzymatically produces angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin converting enzyme. Although angiotensin II increases release of aldosterone from the adrenal cortex, its role in early shock is the increase of arteriolar tone in the mesentery. In addition, arginine vasopressin is released by the posterior pituitary. Arginine vasopressin also increases tone in splanchnic beds [9].Peripheral tissue inflammation can directly stimulate the hypothalamus [10].

Stimulation of the hypothalamus releases catecholamines, glucagon and glucocorticoids.Catecholamines, epinephrine and norepinephrine are important in increasing inotropy,chronotropy and vasoconstriction. In addition, epinephrine potentiates glycogenolysis.Glucagon raises serum concentrations of glucose by stimulating glycogenolysis.Secretion of glucagon increases with secretion of epinephrine and cortisol. Glucocorticoids also stimulate gluconeogenesis and glycogen deposition. The glucocorticoids are implicated in protein catabolism, in which amino acids become substrates for hepatic gluconeogenesis.

These stress hormones are implicated in the relative hyperglycemiaobserved in physiologic stress states[11,12].Other important stimuli that activate the inflammatory response include pain,damage to tissues and microbial invasion. Pain causes neurons to release active peptides.Injury to cells releases formed proteins that stimulate release of cytokines. Included in this group are high mobility group B1 (HMGB1) proteins and heat shock proteins. Microbial products are detected by binding to both soluble and cell surface receptors. The response is rapid.

As Nathan observes, “A rapid response requires sentinel cells pre-stationed in the tissues. Mast cells and macrophages fulfill this function” [8].

Trauma or infection can release neuropeptides that stimulate local mast cells, which,in turn, stimulate other mast cells, nerve endings, endothelium and neutrophils through Gprotein receptors. One consequence of this mechanism is the release of platelet activatingfactor (PAF) by neutrophils. Elaboration of PAF is associated with invasion of extravascular tissues by neutrophils. Neutrophils also are activated by tumor necrosis factor (TNF) and leukotrienes produced by the mast cells. Products of neutrophil activation, including elastase, expose integrins and allow binding of neutrophils to extracellular matrix proteins.

Of importance, the combined signals of integrin binding plus binding of TNF, C5a orother cytokines are required for release of enzymes that cause tissue destruction.If allowed to proceed without regulation, the inflammatory response can produce tissue destruction that is detrimental to the host. This unchecked destruction of tissue is typically prevented by the regulatory steps that are present even in the early stages of inflammation.

At a cellular level, pro-inflammatory agents may change function as the inflammatory response persists. For example, pro-inflammatory products are transformed to anti-inflammatory lipoxins. COX2 converts arachidonate to PGE2, a substance associated with increased capillary permeability.An increase in PGE2 concentrations then provides negative feedback and inhibits COX2. The requirement that combined signals are necessary for release of neutrophil products provides an important level of control. AsNathan observes, “Ongoing infection [is required] to avoid defaulting to the resting state.[8]

Each newly recruited cell generally commits to release pro-inflammatory signalsonly after integrating aspects of both host and microbial origin." This observation has acounterpart in immunology. B cells need antigen receptor binding plus T cell signals tofunction. T cells need antigen receptor binding plus antigen presenting cell (APC)signals and APCs require cytokines plus microbial products or microbial products plusnecrotic host cell products, for the initial inflammatory response to develop into theimmune response.

Controls on the inflammatory process are exerted through the central nervous system. The cholinergic anti-inflammatory pathway inhibits macrophage activation.Experimentally direct stimulation of the vagus nerve inhibits TNF production in organsinnervated by the vagus, including liver, lung, spleen, kidney and gut. Release of acetylcholine has been demonstrated to inhibit activation of the macrophages [13].

When ordered, the inflammatory response can limit the spread of infection, limittissue damage and repair tissues. The forces that convert the ordered and regulated inflammatory process into one that produces ongoing tissue damage are not well understood.

Current understanding of the pathogenesis of organ failure in sepsis involves several steps: host recognition of microbes or foreign tissue, signal amplification, the counter-inflammatory response and the coagulation cascade[14] .

Recognition of Microbes or Foreign Tissue:

Many endogenous and exogenous mediators of inflammatory states have been studied inhuman, experimental animal and in vitro systems. The generalized Shwartzman reactionprovides an important clue. In the generalized Shwartzman reaction, two doses of endotoxin are administered to the same animal, usually a rabbit, 24 h apart. If both doses are given intravenously, a shock state may be produced that

is often accompanied by disseminated intravascular coagulation. If the first dose is given intradermally and the second dose given intravenously, a hemorrhagic reaction occurs at the site of the dermal injection, the local Shwartzman reaction. The observation that enterobacteriaceal endotoxin [lipopolysaccharide (LPS)] was the mediator of the shock state seen in the generalized Shwartzman reaction led to the identification of the signaling receptor complex for endotoxin, which consists of toll-like receptor 4 (TLR4), LPS-binding protein and the opsonic receptor CD14 [15.16].

Remarkably, members of the toll-like receptor family bind a widerange of ligands and have proved to be the primary signaling molecules for mostinflammatory stimuli, including Gram-negative and Gram-positive bacterial toxins, bacterial DNA, fungal elements, and even endogenous products of cellular injury and death .These acts of immune recognition of toxic nonself products are fundamental to the innate immune system and act prior to the organization of cellular or humoral immunity.

Indeed the recognition of nonself by the macrophage (mediated ultimately throughthe toll-like receptor system) acts to stimulate and coordinate the development of cellularand humoral responses to a significant infectious challenge.

Thus the physiologic pathway that mediates inflammatory signaling in response to and clearance of LPS may serve as a model for understanding the response to an inflammatory challenge. Figure 2 illustrates the known components of cell surface recognition of LPS.known components of cell surface recognition of LPS. Experimental models, both in vitro and in vivo, have demonstrated that alteration of function of any of a number of proteins in the extracellular serum or at the cell surface will perturb physiologic inflammatory signaling by TLR4 in response to LPS. Significant inflammatory blockade achieved by directed immune modulation resulted in increased survival in response to toxic challenge with LPS but decreased survival

in response to an infectious challenge, such as experimental peritonitis. These indicate that intact innate immune signaling is required for a vigorous host response to infection but may become deleterious with prolonged exposure to a toxic stimulus. Genetic polymorphisms of TLR4 and the associated protein, CD14, have both been associated with altered susceptibility to Gram-negative infection and septic shock, a finding that supports the importance of this pathway in clinically significant disease.

Signal Amplification:

From the activation of TLR4 at the macrophage cell surface, the inflammatory signal istransduced to the nucleus via a series of protein–protein interactions that alter gene transcription and production of inflammatory mediators [17,18]. Mononuclear cells produceinterleukin-1 (IL-1), IL-6, and TNF~in addition to other cytokines. These pro-inflammatory cytokines are released early, mimic many features of LPS administration and stimulate inflammatory cell migration into tissues. Several of these mediators such as (TNF*a*) and IL-1 have been extensively studied but immune modulatory strategies aimed at blocking these mediators in patients with severe sepsis or septic shock have been unsuccessful.Two other macrophage derived products may prove to be useful clinical targets for therapy. HMGB1 is anonhistone chromosomal protein that is implicated in stabilizing nucleosomes, gene transcription and modulating steroid receptors.[14]

Counter-Inflammatory Response:

After initial inflammatory activation, the release of mediators produces activated neutrophils that can swarm to the site of infection to eradicate the invaders. These cells produce toxic proteins, peptides and reactive oxygen species that not only kill pathogenic organisms but also can cause collateral damage to host cells. Activated neutrophils also are trapped in pulmonary capillary beds as well as in post-capillary

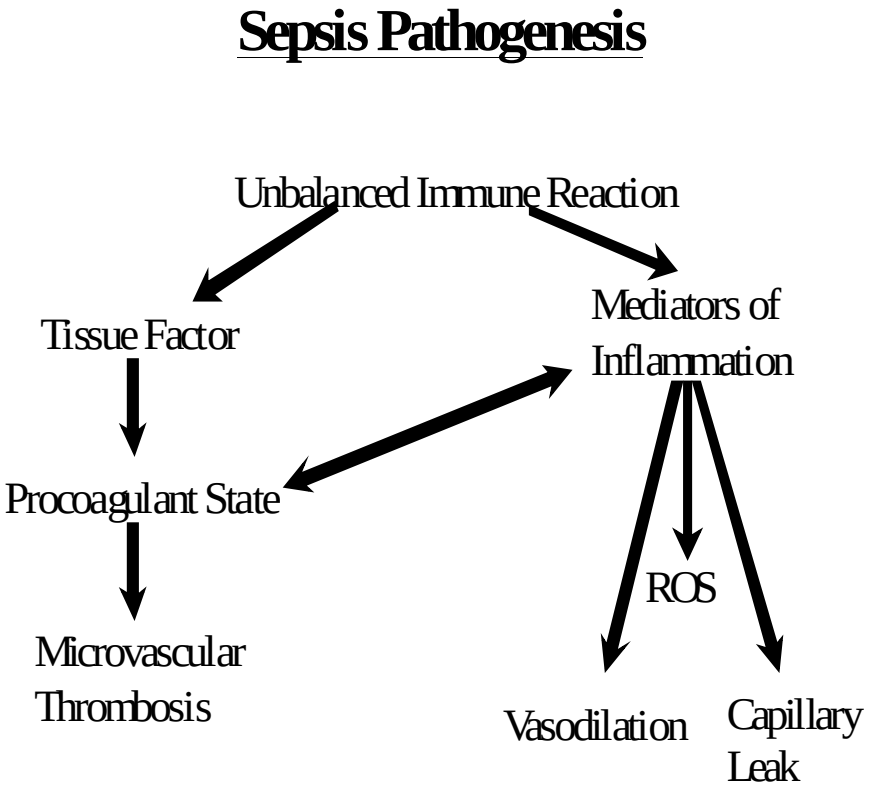
venules of othertissues. Damage to these tissues attracts additional immune cells and the unregulatedamplification of this process may lead to organ failure distant from the site of the originalinfection. The down-regulation of these activated neutrophils is believed to be related toneutrophil apoptosis [19]. Pro and counter-inflammatory signals within the activatedneutrophil are targets of study [20].

IL-10, an anti-inflammatory mediator, has been studied in animal models and inclinical trials with mixed results. These investigations indicate that the timing of IL-10production (oradministration) is crucial to its effectiveness—too early or too late inrelation to an infectious challenge and the effect is counter-productive [21,22].

The Coagulation Cascade:

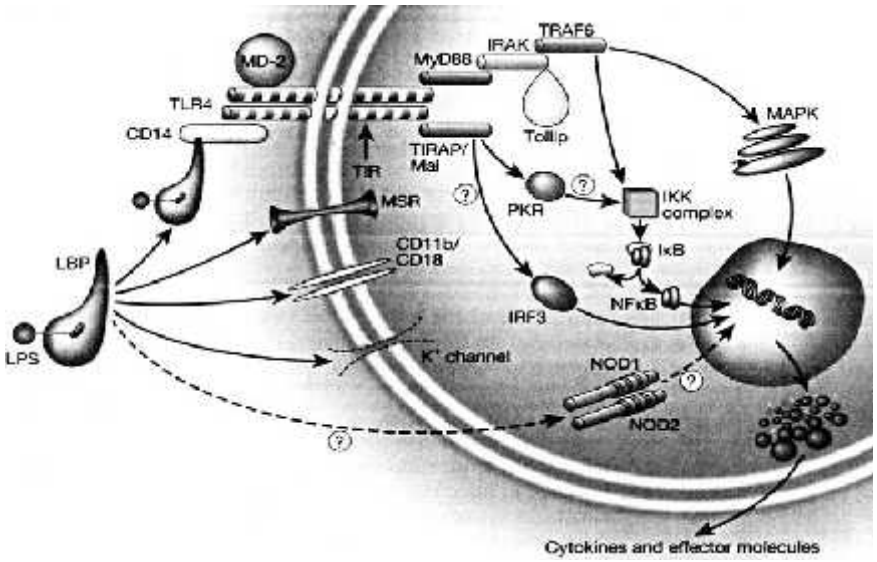
With local and systemic inflammation comes microvascular coagulation. Endothelialdamage exposes tissue factor (TF) to intravascular factor VII with resultant activationof the extrinsic pathway of coagulation . Sepsis drives expression of TF onendothelial and monocyte cell surfaces, a process that amplifies microvascularprocoagulantsignaling. Down-regulation of this system is largely mediated by anti-thrombin and byactivated protein C (aPC). Failure of the down-regulatory mechanisms can lead to thepectacular morbidity seen in Meningococcal purpurafulminans and presumably tomuch of the organ dysfunction seen in patients with adult respiratory distress syndromeand acute renal failure. The recent clinical trial of aPC in patients with severe sepsisand organ dysfunction produced a measurable improvement in mortality [23,24.]

Figure -1



Reference-hooper sepsis management [25]

Figure 2



Cell-surface recognition of LPS(lipo polysaccharide). [14]

The principal mechanism by which LPS is sensed is via an LPS-binding protein (LBP)–LPS complex and then signalling through the TLR4–MD-2 complex.However, other cell surface molecules also sense LPS; these include the macrophage scavenger receptor (MSR), CD11b/CD18 and ion channels. Intracellular signalling depends on binding of the intracellular TLR domain, TIR (Toll/IL-1 receptor homology domain) to IL-1 receptor-associated kinase (IRAK), a process that is facilitated by two adapter proteins, MyD88 (myeloid differentiation protein 88) and TIRAP [TIR domain-containing adapter protein; also called MyD88- adapter-like protein (Mal)], and inhibited by a third protein Tollip (Toll-interacting protein). Note that there is also an MyD88-independent pathway by which TIRAP/Mal signals through an RNAdependent protein kinase (PKR) and interferon regulatory factor (IRF)-3. Recently, it has been proposed that cells may also be able to respond to LPS by intracellular receptors called NOD proteins (for nucleotide-binding oligomerization domain). NOD1 (also called caspase-recruitment domain 4) was identified originally on the basis of structural homology to the apoptosis regulator,

Apaf-1. The NOD proteins have some similarities to the resistance (R) genes in plants that are involved in pathogen recognition; in common with TLRs and R genes, NODs have leucine-rich repeats. Expression of NOD1 and NOD2 confer responsiveness to Gram-negative LPS but not to lipoteichoic acid, which is found in Gram-positive bacteria. The mechanism by which NOD may recognize LPS in the cytosol is unknown.[14]

CONCEPTUAL HYPOTHESES:

As briefly outlined earlier, our understanding of the molecular and cellular events leadingfrom an infectious or inflammatory stimulus to local and systemic host injury have beenvastly expanded over the last decade [14]. Yet the progression from a single illness orinjury to MOF often occurs without clear cause. Several hypotheses have beenproposed to account for the development of the syndrome of MOF in such patients.The two-hit hypothesis reflects the clinical and experimental observations that asingle inflammatory insult may prime the host response and make the host response tothe next challenge exaggerated and potentially counter-productive [26]. For example,pneumonia or an episode of catheter sepsis that might ordinarily be well tolerated producesa profound inflammatory response with progressive organ failure. This hypothesis grew fromobservations in trauma patients with early and late MOF. Early MOF resulted from a massive injury; whereas, late MOF appeared to develop after a significantly lesser perturbation in a patient who had already suffered a primary injury[27] .

Specific modifications of current therapy may influence the amount of "priming" that takes place and leave patients less vulnerable to subsequent nosocomial infection. For example, the use of hypertonic saline for resuscitation may be beneficial [28]. Improved understanding of the molecular mechanisms of priming

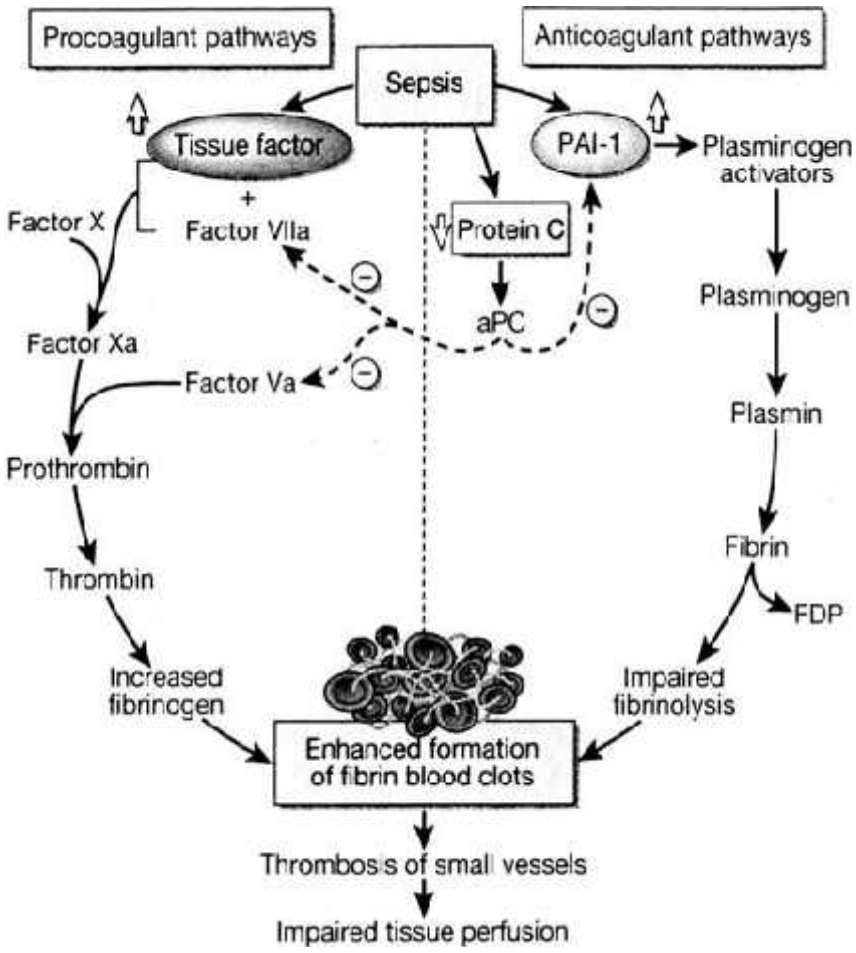
may allow prophylactic immunomodulation in patients who have already suffered a first “hit.”The gut translocation hypothesis states that the alimentary tract serves as a repository for vast quantities of bacteria, fungi, and microbial toxins that access the systemic circulation under conditions of increased intestinalpermeability during critical illness [29,30]. This phenomenon results in ongoing systemic infection and inflammation via toxins that produce MOF. This hypothesis is quite controversial. Selective decontamination of the GI tract with oral antibiotics in hopes of decreasing the nosocomial infectionsthat were thought to emanate from the gut have not consistently improved mortality.

Metaanalyses suggest a mortality benefit of 10%, despite a decrease in hospital acquiredinfection, in combined medical and surgical intensive care populations[31] . Anotherrecent meta-analysis suggests that gut decontamination may be beneficial in surgicalpatients [32]. In a series of studies, Deitch[33] has shown that mesenteric lymph collectedafter hemorrhagic shock is an inflammatory stimulus and can cause neutrophil activationand endothelial injury. These data support a potential role for the gut as a “motor of sepsis” that does not depend on ongoing translocation of pathogenic microorganisms to the systemic circulation.

The immune paralysis hypothesis states that an inflammatory insult produces both asystemic inflammatory response and a compensatory anti-inflammatory response. Undercertain conditions, the anti-inflammatory response is excessive and leads to immunefailure and heightened susceptibility to nosocomial infection[34]. Other potential markers of immune failure in trauma patients include decreased immunoglobulin levels, decreased opsonization activity of plasma and suppressed MHC class 2 antigen expression on circulating monocytes [35]. These findings correlate with a shift in T cells toward the Th2 phenotype, which is predominantly anti-

inflammatory [36]. The degree to which this phenotypic shift in T lymphocyte activity is adaptive, and how much may represent overcompensation and immune failure, is not presently known. Studies are ongoing to examine and potentially modulate the molecular mechanisms responsible for this shift.

Figure -3



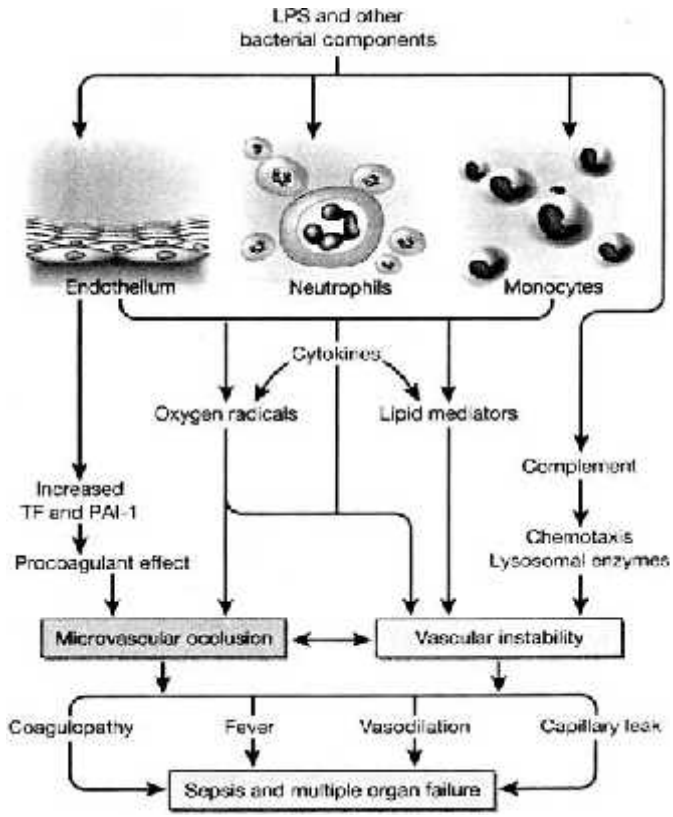
The Coagulation Cascade

Sepsis disturbs the normal homeostatic balance between procoagulant and anticoagulantmechanisms. Tissue factor expression is enhanced leading to increased production of prothrombin that is converted to thrombin and that in turn generates fibrin from fibrinogen. Simultaneously, levels of the plasminogen-activator inhibitor-1 (PAI-1) are increased, resulting in impaired production of plasmin and thus failure

of normal fibrinolytic mechanisms by which fibrin is converted to degradation products (FDP). Sepsis also causes a fall in the levels of the natural anticoagulant protein C.[14]

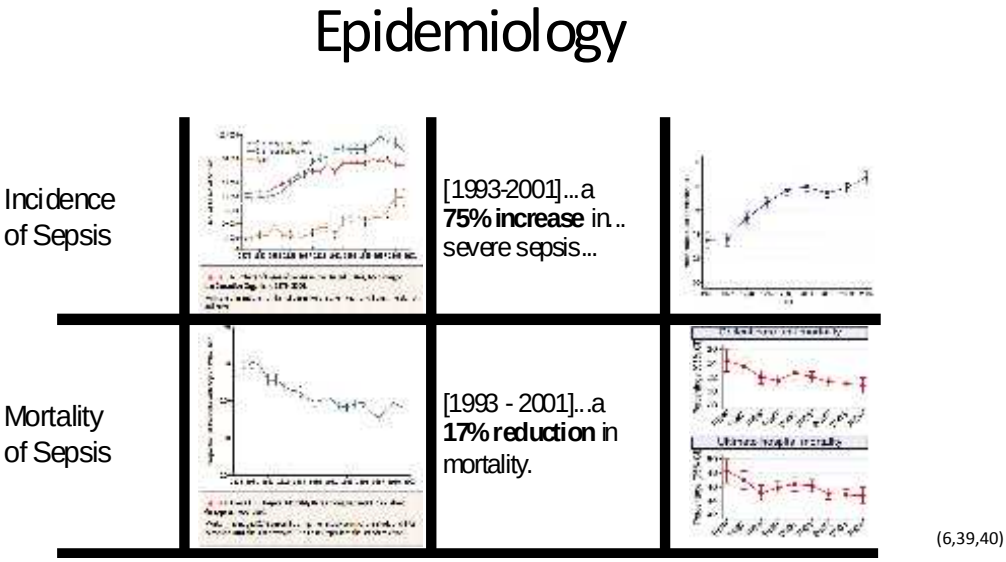
The activated form of protein C, aPC, dissociates from the endothelial protein C receptor to inactive factor Va and VIIa and inhibit PAI-1 activity; hence reduced levels of protein C result in further procoagulant effect. The net result is enhanced formation of fibrin clots in the microvasculature, leading to impaired tissue oxgenation and cell damage.

Figure-4



Pathogenetic networks in shock. LPS and other microbial components simultaneouslyactivate multiple parallel cascades that contribute to the pathophysiology of adult respiratorydistress syndrome (ARDS) and shock. The combination of poor myocardial contractility,impaired peripheral vascular tone and microvascular occlusion leads to tissue hypoperfusion andinadequate oxygenation, and thus to organ failure[14].

Figure-5



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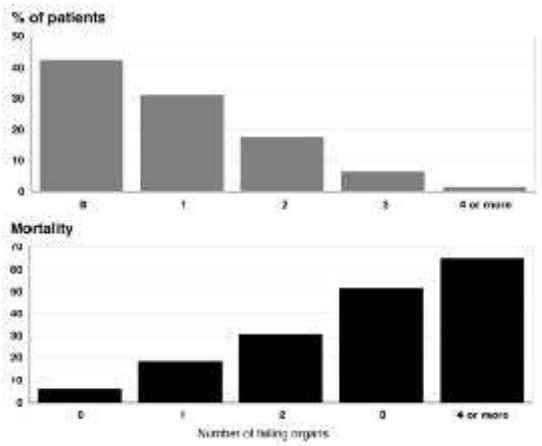
Epidemiology Of Sepsis

Figure-6



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REVISED DIAGNOSTIC CRITERIA FOR SEPSIS:

GENERAL VARIABLES:

- Fever(core temperature >38.3^0 C
- Hypothermia (core temperature <36^0 C
- Heart rate >90 bpm or >2 SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (>20 ml/kg over 24 hrs).
- Hyperglycemia (plasma glucose > 120 mg/dl or 7.7 mmol/ltr) in the absence of diabetes.

INFLAMMATORY VARIABLES:

- Leucocytosis(WBC count >12000 cells/ micro ltr)
- Leucopenia (WBC count <4000 cells/ micro ltr)
- Normal WBC with more than 10 % immature forms.
- Plasma C reactive protein >2 SD above the normal value
- Plasma pro calcitonin >2 SD above the normal value.

HEMODYNAMIC VARIABLES:

- Arterial hypotension (SBP <90mm Hg, MAP<70 mmHg, or an SBP decrease > 40 mm Hg in adults or <2 SD below normal for age)
- Mixed venous oxygen saturation > 70 % in adults.
- Cardiac index> 3.5 ltrs /min/ m^2

ORGAN DYSFUNCTION VARIABLES:

- Arterial hypoxemia (Pa O2/ FiO2<300)
- Acute oliguria (urine output <0.5 ml /kg/ hr or 45mmol/ltr for atleast 2 hrs.)
- Creatinine increase >0.5 mg/dl
- Coagulation abnormalities (INR>1.5 otaPTT> 60 secs).

- Ileus (absent bowel sounds).
- Thrombocytopenia (platelet count < 100000 cells /micro ltr)
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/ltr)

TISSUE PERFUSION VARIABLES:

- Hyperlactateimia(>1mmol/ltr)
- Decreased capillary refill or mottling[37].

SEVERE SEPSIS:

Severe sepsis definition= sepsis induced tissue hypoperfusion or organ dysfunction(any of the following thought to be due to the infection.)

- Sepsis induced hypotension
- Lactate above upper limits laboratory normal
- Urine output<0.5ml/kg/hr for more than 2 hrs despite adequate fluid resuscitation
- Acute lung injury with Pa O2/FiO2<250 in the absence of pneumonia as infection source
- Acute lung injury with PaO2/FiO2<200 in the presence of pneumonia as infection source
- Creatinine>2.0 mg/dl
- Bilirubin >2 mg/dl
- Platelet count <100000microltr
- Coagulopathy (inr>1.5)[38]

THERAPEUTIC PRIORITIES :

The early administration of fluids and antibiotics is the cornerstone of management for patients with sepsis and septic shock.

Therapeutic priorities for patients with sepsis or septic shock include:

- Early initiation of supportive care to correct physiologic abnormalities such as hypoxemia and hypotension.
- Distinguishing sepsis from systemic inflammatory response syndrome (SIRS) because if an infection exists it must be identified and treated as soon as possible. This may require appropriate antibiotics as well as a surgical procedure (eg, drainage).

EARLY MANAGEMENT — The first priority in any patient with sepsis or septic shock is stabilization of their airway and breathing. Next, perfusion to the peripheral tissues should be restored and antibiotics administered.

Stabilize respiration — Supplemental oxygen should be supplied to all patients with sepsis and oxygenation should be monitored continuously with pulse oximetry. Intubation and mechanical ventilation may be required to support the increased work of breathing that typically accompanies sepsis or for airway protection since encephalopathy and a depressed level of consciousness frequently complicate sepsis.

Assess perfusion — Once the patient's respiratory status has been stabilized, the adequacy of perfusion should be assessed. Hypotension is the most common sign but critical hypoperfusion can also occur in the absence of hypotension, especially during early sepsis. Clinical signs of impaired perfusion include the following:

Hypotension – Hypotension is the most common indicator that perfusion is inadequate (eg, systolic blood pressure [SBP] <90 mmHg, mean arterial pressure <70 mmHg, decrease in SBP >40 mmHg). Therefore, it is important that the blood pressure be assessed early and often. Because a sphygmomanometer may be unreliable in hypotensive patients, an arterial catheter may be inserted if blood pressure is labile or restoration of arterial perfusion pressures is expected to be a protracted process. Attempts to insert an arterial line should not delay the prompt management of shock.

Signs of poor end-organ perfusion – Warm, flushed skin may be present in the early phases of sepsis. As sepsis progresses to shock, the skin may become cool due to redirection of blood flow to core organs. Additional signs of hypoperfusion include tachycardia >90 per min, obtundation or restlessness and oliguria or anuria.

These findings may be modified by preexisting disease or medications. As examples, older patients, diabetic patients and patients who take beta-blockers may not exhibit an appropriate tachycardia as blood pressure falls. In contrast, younger patients frequently develop a severe and prolonged tachycardia and fail to become hypotensive until acute decompensation later occurs, often suddenly. Patients with chronic hypertension may develop critical hypoperfusion at a higher blood pressure than healthy patients (ie. relative hypotension).

Elevated lactate – An elevated serum lactate (eg.>2 mmol/L) can be a manifestation of organ hypoperfusion in the presence or absence of hypotension and is an important component of the initial evaluation, since elevated lactate is associated with poor prognosis. A serum lactate level ≥4 mmol/L is consistent with and diagnostic of septic shock. Additional laboratory studies that help characterize the severity of sepsis

include low platelet count and elevated international normalized ratio, creatinine and bilirubin.

Establish venous access — Venous access should be established as soon as possible inpatients with suspected sepsis. While peripheral venous access may be sufficient in somepatients particularly for initial resuscitation, the majority will require central venous access at some point during their course. A central venous catheter (CVC) can be used to infuseintravenous fluids, medications (particularly vasopressors) and blood products, as well as to draw blood for frequent laboratory studies. In addition, this access can be used forhemodynamic monitoring by measuring the central venous pressure (CVP) and the central venous oxyhemoglobin saturation ($ScvO_2$).

Interventions to restore perfusion — The rapid restoration of perfusion is predominantly achieved by the administration of intravenous fluids, usually crystalloids. Modalities such as vasopressor therapy, inotropic therapy and blood transfusion are added, depending on the response to fluid resuscitation, evidence for myocardial dysfunction and presence of anemia.

Intravenous fluids — In patients with sepsis, intravascular hypovolemia is typical and may be severe requiring rapid fluid resuscitation.

Volume -Fluid therapy should be administered in well-defined (eg, 500 mL) rapidly infused boluses . Volume status, tissue perfusion, blood pressure and the presence or absence of pulmonary edema must be assessed before and after each bolus. Intravenous fluid challenges can be repeated until blood pressure and tissue perfusion are acceptable, pulmonary edema ensues or fluid fails to augment perfusion.

Careful monitoring is essential because patients with sepsis may develop noncardiogenic pulmonary edema (ie, acute respiratory distress syndrome [ARDS]). Once patients with ARDS have been fluid resuscitated a liberal approach to intravenous fluid administration has been shown to prolong the duration of mechanical ventilation.

Vasopressors — Vasopressors are second line agents in the treatment of sepsis and septic shock; we prefer intravenous fluids as long as they increase perfusion without seriously impairing gas exchange.However, intravenous vasopressors are useful in patients who remain hypotensive despite adequate fluid resuscitation or who develop cardiogenic pulmonary edema.

Inotropic therapy-. Dobutamine is the usual inotropic agent. At low doses, dobutamine may cause the blood pressure to decrease because its peripheral effects can dilate the systemic arteries. However, as the dose is increased, blood pressure usually rises because cardiac output increases out of proportion to the fall in peripheral vascular resistance.

Goals of initial resuscitation — The goal of fluid resuscitation is early restoration of perfusion to prevent or limit multiple organ dysfunction, as well as to reduce mortality.

The term "early goal-directed therapy" (EGDT) refers to the administration of intravenous fluids within **the first six hours of presentation** using physiologic targets to guide fluid management.

Early goal-directed therapy targets —

- Mean arterial pressure (MAP) ≥65 mmHg (MAP = [(2 x diastolic) + systolic]/3)
- Urine output ≥0.5 mL/kg/hour
- Static or dynamic predictors of fluid responsiveness, eg, CVP 8 to 12 mmHg when central access is available (static measurement) or respiratory changes in the radial artery pulse pressure (dynamic measurement).
- Central venous (superior vena cava) oxyhemoglobin saturation ($ScvO_2$) ≥70 percent (when central access is available) or mixed venous oxyhemoglobin saturation (SvO_2) ≥65 percent (if a pulmonary artery catheter is being used).

Lactate clearance should be followed as a target in patients with sepsis to ensure a trend that demonstrates adequate clearance with therapy. Newer point of care analyzers are commercially available that may allow clinicians to follow lactate levels at the bedside more readily.

Evidence that supports the use of EGDT targets is described below:

CVP, MAP and urine output – CVP 8 to 12 mmHg, MAP ≥65 mmHg and urine output ≥0.5 mL/kg per hour are common EGDT targets used in clinical practice.

Lactate clearance – The lactate clearance is defined by the equation [(initial lactate - lactate >2 hours later)/initiallactate] x 100. The lactate clearance and interval change inlactate over the first 24-48 hours of resuscitation has been evaluated as a potential marker for effective resuscitation.

Timing and duration — The early administration of fluid appears to be more important than volume or type of fluid in reducing mortality associated with sepsis. Once the targets of resuscitation are met and perfusion is restored, fluids can be

reduced or stopped, and occasionally patients can be diuresed, when necessary. Resolution of sepsis and septic shock can take as little as a few hours or can be protracted to days or weeks.

There are two possible outcomes following the interventions described above:

Inadequate perfusion – Despite aggressive therapy, the patient may have persistent hypoperfusion and progressive organ failure. This should prompt reassessment of the adequacy of the above therapies, antimicrobial regimen and control of the septic focus, as well as the accuracy of the diagnosis and the possibility that unexpected complications or coexisting problems have intervened (eg. pneumothorax following CVC insertion).

Adequate perfusion – Patients who respond to therapy should have the rate of fluid administration reduced or stopped, and vasopressor support weaned. Patients should also continue to have their clinical and laboratory parameters followed closely. These include blood pressure, arterial lactate, urine output, creatinine, platelet count, Glasgow coma scale score, serum bilirubin, liver enzymes, oxygenation (ie, arterial oxygen tension or oxyhemoglobin saturation) and gut function. Reevaluation is indicated if any of these parameters worsen or fail to improve.

CONTROL OF THE SEPTIC FOCUS — Prompt identification and treatment of the primary site or sites of infection are essential. This is the primary therapeutic intervention, with most other interventions being purely supportive. Antibiotics should be administered within the first six hours of presentation or earlier.

Identification of the septic focus — A careful history and physical examination may yield clues to the source of sepsis and help to guide microbiologic evaluation . As an example, sepsis arising after trauma or surgery is often due to infection at the site of

injury or surgery. The presence of a urinary or vascular catheter increases the chances that these are the source of sepsis.

Gram stain of material from sites of possible infection may give early clues to the etiology of infection while cultures are incubating. As examples, urine should be routinely analyzed via dipstick for leukocyte esterase, gram stained and cultured; sputum should be examined in a patient with a productive cough; and an intra-abdominal collection in a postoperative patient should be percutaneously sampled under ultrasound or other radiologic guidance[42].

Blood should be drawn from two distinct venipuncture sites and inoculated into standard blood culture media (aerobic and anaerobic). For patients with a vascular catheter, blood should be obtained both through the catheter and from another site[43].

There is no single test that immediately confirms the diagnosis of severe sepsis or septic shock. However, several laboratory tests, all of which are still investigational, have been studied as diagnostic markers of active bacterial infection[44]:

- Elevated serum procalcitonin levels are associated with bacterial infection and sepsis[45,46] .
- The plasma concentration of soluble TREM-1 (triggering receptor expressed on myeloid cells), a member of the immunoglobulin superfamily that is specifically upregulated in the presence of bacterial products, is increased in patients with sepsis . In a small trial, increased TREM-1 levels were both sensitive and specific for the diagnosis of bacterial sepsis. However, a subsequent prospective cohort study found that increased TREM-1 levels

predicted sepsis with a sensitivity and specificity of only 53 and 86 percent, respectively . Serial monitoring of TREM-1 may also provide prognostic information in patients with established sepsis.[47,48]

- Increased expression of CD64 on polymorphonuclear leukocytes indicates cellular activation and has been shown to occur in patients with sepsis[49,50] .

The combination of procalcitonin levels, TREM-1 levels, and CD64 expression appears to be superior to the use of any of these markers alone. However, evaluation of the clinical usefulness of such biomarkers is still in its early stages and should be considered preliminary.

Eradication of infection — Prompt and effective treatment of the active infection is essential to the successful treatment of sepsis and septic shock[43]. Source control (physical measures undertaken to eradicate a focus of infection and eliminate or treat ongoing microbial proliferation and infection) should be undertaken since undrained foci of infection may not respond to antibiotics alone. As examples, potentially infected foreign bodies (eg. vascular access devices) should be removed when possible and abscesses should undergo percutaneous or surgical drainage.

Antimicrobial regimen — Intravenous antibiotic therapy should be initiated within the first six hours or earlier (eg, within one hour), after obtaining appropriate cultures, since early initiation of antibiotic therapy is associated with lower mortality[51,52]. The choice of antibiotics can be complex and should consider the patient's history (eg, recent antibiotics received)[53], comorbidities, clinical context (eg. community- or hospital-acquired), Gram stain data, and local resistance patterns[54,55,56].

Poor outcomes are associated with inadequate or inappropriate antimicrobial therapy.[57,58] They are also associated with delays in initiating antimicrobial therapy, even short delays (eg. an hour).

When the potential pathogen or infection source is not immediately obvious, we favor broad-spectrum antibiotic coverage directed against both gram-positive and gram-negative bacteria. Few guidelines exist for the initial selection of empiric antibiotics in severe sepsis or septic shock.

Staphylococcus aureus is associated with significant morbidity if not treated early in the course of infection [59]. There is growing recognition that methicillin-resistant S. aureus (MRSA) is a cause of sepsis not only in hospitalized patients, but also in community dwelling individuals without recent hospitalization.[60,61]

Regardless of the antibiotic regimen selected, patients should be observed closely for toxicity, evidence of response and the development of nosocomial superinfection.[62]The duration of therapy is typically 7 to 10 days, although longer courses may be appropriate in patients who have a slow clinical response, an undrainable focus of infection or immunologic deficiencies[63]. In patients who are neutropenic, antibiotic treatment should continue until the neutropenia has resolved or the planned antibiotic course is complete, whichever is longer. In non-neutropenic patients in whom infection is thoroughly excluded, antibiotics should be discontinued to minimize colonization or infection with drug-resistant microorganisms and superinfection with other pathogens.

ADDITIONAL THERAPIES

Glucocorticoids — Glucocorticoids have long been investigated as therapeutic agents in sepsis because the pathogenesis of sepsis involves an intense and potentially deleterious host inflammatory response. Evidence from randomized trials suggest that corticosteroid therapy is most likely to be beneficial in patients who have severe septic shock (defined as a systolic blood pressure <90 mmHg) that is unresponsive to adequate fluid resuscitation and vasopressor administration.

Nutrition — There is consensus that nutritional support improves nutritional outcomes in critically ill patients, such as body weight and mid-arm muscle mass.

Venous thromboembolism prophylaxis — Patients with sepsis and septic shock are at increased risk for venous thromboembolism such that patients should receive thromboprophylaxis.

Intensive insulin therapy — Hyperglycemia and insulin resistance are common in critically ill patients, independent of a history of diabetes mellitus . The optimal blood glucose range is between 140 and 180 mg/dL (7.7 to 10 mmol/L).

External cooling or antipyretics — Controlling fever during sepsis and septic shock has potential benefits and adverse effects, the net effects of which are uncertain.

External cooling consists of using either an automatic cooling blanket, or ice-cold bed sheets and ice packs, to achieve a core body temperature of 36.5 to 37°C for 48 hours. It decreases the time to fever control without exposing the patient to potential adverse effects of antipyretic drugs[42].

Recommendations: Initial Resuscitation and Infection Issues

A. Initial Resuscitation

1. Protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L).

Goals during the first 6 hrs of resuscitation:

- Central venous pressure 8–12 mm Hg
- Mean arterial pressure (MAP) ≥ 65 mm Hg
- Urine output ≥ 0.5 mL/kg/hr
- Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%respectively .
- In patients with elevated lactate levels targeting resuscitation to normalize lactate .

B. Screening for Sepsis and Performance Improvement:

1. Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy .

2. Hospital–based performance improvement efforts in severe sepsis.

C. Diagnosis:

1. Cultures as clinically appropriate before antimicrobial therapy if no significant delay (> 45 mins) in the start of antimicrobial(s). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawnpercutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 hrs) inserted.

2. Use of the 1,3 beta-D-glucan assay, mannan and anti-mannan antibody assays , if available and invasive candidiasis is in differential diagnosis of cause of infection.
3. Imaging studies performed promptly to confirm a potential source of infection .

D. Antimicrobial Therapy:

1. Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock and severe sepsis without septic shock as the goal of therapy.
2. Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis .
3. Antimicrobial regimen should be reassessed daily for potential deescalation .
4. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection .
5. Combination empirical therapy for neutropenic patients with severe sepsis and for patients with difficult-to-treat, multidrugresistant bacterial pathogens such as Acinetobacterand Pseudomonas spp.
6. For patients with severe infectionsassociated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for P. aeruginosabacteremia . A combination of beta-lactam and macrolide for patients with septic shock from bacteremicStreptococcus pneumoniaeinfections .

7. Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known.
8. Duration of therapy typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus;* some fungal and viral infections or immunologic deficiencies, including neutropenia .
9. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin.
10. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause .

E. Source Control:

1. A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible and intervention be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible.

2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred .

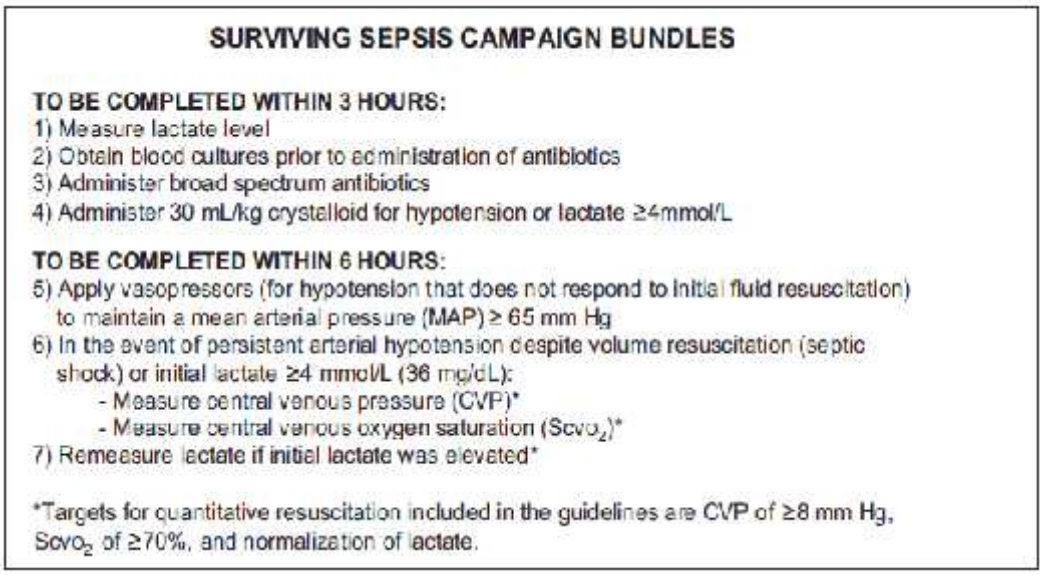
3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (eg. percutaneous rather than surgical drainage of an abscess) .

4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established .

F. Infection Prevention:

1. Selective oral decontamination and selective digestive decontamination should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia; This infection control measure can then be instituted in health caresettings and regions where this methodology is found to be effective .
2. Oral chlorhexidinegluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis.

FIGURE-7



SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4mmol/L

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

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G. Fluid Therapy of Severe Sepsis:

- Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock .
- Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock .

- Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids .
- Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients
- Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables .

H. Vasopressors:

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg.
2. Norepinephrine as the first choice vasopressor .
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure .
4. Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage.
5. Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) .
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) .

7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target.
8. Low-dose dopamine should not be used for renal protection .
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available.

I. Inotropic Therapy:

1. A trial of dobutamine infusion up to 20 micrograms/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP .
2. Not using a strategy to increase cardiac index to predetermined supranormallevels .

J. Blood Product Administration:

1. Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severehypoxemia, acute hemorrhage or ischemic heart disease, we recommend that red blood cell transfusion occur only whenhemoglobin concentration decreases to <7.0 g/dL to target a hemoglobin concentration of 7.0 –9.0 g/dL in adults .
2. Not using erythropoietin as a specific treatment of anemia associated with severe sepsis .

3. Fresh frozen plasma not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasiveprocedures .
4. Not using antithrombin for the treatment of severe sepsis and septic shock .
5. In patients with severe sepsis, administer platelets prophylactically when counts are <10,000/mm3 (10 x 109/L) in the absenceof apparent bleeding. We suggest prophylactic platelet transfusion when counts are < 20,000/mm3 (20 x 109/L) if the patienthas a significant risk of bleeding. Higher platelet counts (≥50,000/mm3 [50 x 109/L]) are advised for active bleeding, surgeryor invasive procedures.

K. Mechanical Ventilation of Sepsis-Induced Acute Respiratory Distress Syndrome (ARDS):

1. Target a tidal volume of 6 mL/kg predicted body weight in patients with sepsis-induced ARDS.
2. Plateau pressures be measured in patients with ARDS and initial upper limit goal for plateau pressures in a passively inflatedlung be ≤30 cm H2O.
3. Positive end-expiratory pressure (PEEP) be applied to avoid alveolar collapse at end expiration (atelectotrauma).
4. Strategies based on higher rather than lower levels of PEEP be used for patients with sepsis- induced moderate or severeARDS .
5. Recruitment maneuvers be used in sepsis patients with severe refractory hypoxemia.
6. Prone positioning be used in sepsis-induced ARDS patients with a Pao2/Fio2 ratio ≤ 100 mm Hg in facilities that haveexperience with such practices.

7. Mechanically ventilated sepsis patientsto be maintained with the head of the bed elevated to 30-45 degrees to limitaspiration risk and to prevent the development of ventilator-associated pneumonia.
8. Noninvasive mask ventilation (NIV) to be used in the minority of sepsis-induced ARDSpatients in whom the benefits of NIVhave been carefully considered and are thought to outweigh the risks .
9. Weaning protocol to be in place and the mechanically ventilated patients with severe sepsis undergo spontaneousbreathing trials regularly to evaluate the ability to discontinue mechanical ventilation when they satisfy the following criteria: a)arousable; b) hemodynamically stable (without vasopressor agents); c) no new potentially serious conditions; d) low ventilator and end-expiratory pressure requirements; and e) low Fio2 requirements which can be met safely delivered with a face mask ornasal cannula. If the spontaneous breathing trial is successful, consideration should be given for extubation.
10. Against the routine use of the pulmonary artery catheter for patients with sepsis-induced ARDS .
11. A conservative rather than liberal fluid strategy for patients with established sepsis-induced ARDS who do not have evidence oftissue hypoperfusion .
12. In the absence of specific indications such as bronchospasm, not using beta 2-agonists for treatment of sepsis-induced ARDS.

L. Sedation, Analgesia and Neuromuscular Blockade in Sepsis:

1. Continuous or intermittent sedation be minimized in mechanically ventilated sepsis patients, targeting specific titration endpoints .
2. Neuromuscular blocking agents (NMBAs) be avoided if possible in the septic patient without ARDS due to the risk ofprolonged neuromuscular blockade

followingdiscontinuation. If NMBAs must be maintained, either intermittent bolus asrequired or continuous infusion with train-of-four monitoring of the depth of blockade should be used.

3. A short course of NMBA of not greater than 48 hours for patients with early sepsis-induced ARDS and a Pao2/Fio2< 150 mm Hg .

M. Glucose Control:

1. A protocolized approach to blood glucose management in ICU patients with severe sepsis commencing insulin dosing when2 consecutive blood glucose levels are >180 mg/dL. This protocolized approach should target an upper blood glucose≤180 mg/dL rather than an upper target blood glucose ≤ 110 mg/dL.
2. Blood glucose values be monitored every 1–2 hrs until glucose values and insulin infusion rates are stable and then every 4 hrsthereafter.
3. Glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution, as such measurements may notaccurately estimate arterial blood or plasma glucose values .

N. Renal Replacement Therapy:

1. Continuous renal replacement therapies and intermittent hemodialysis are equivalent in patients with severe sepsis and acuterenal failure.
2. Use continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patients .

O. Deep Vein Thrombosis Prophylaxis:

1. Patients with severe sepsis receive daily pharmacoprophylaxis against venous thromboembolism (VTE). This shouldbe accomplished with daily subcutaneous low-molecular weight heparin (LMWH) . If creatinine clearance is <30 mL/min, use dalteparin or another form of LMWH thathas a low degree of renal metabolism or UFH (Un fractionised heparin).
2. Patients with severe sepsis be treated with a combination of pharmacologic therapy and intermittent pneumatic compressiondevices whenever possible.
3. Septic patients who have a contraindication for heparin use (eg, thrombocytopenia, severe coagulopathy, active bleeding, recentintracerebral hemorrhage) not receivepharmacoprophylaxis , but receive mechanical prophylactic treatment, suchas graduatedcompression stockings or intermittent compression devices,unless contraindicated. When the riskdecreases start pharmacoprophylaxis.

P. Stress Ulcer Prophylaxis:

1. Stress ulcer prophylaxis using H2 blocker or proton pump inhibitor be given to patients with severe sepsis/septic shock whohave bleeding risk factors .
2. When stress ulcer prophylaxis is used, proton pump inhibitors rather than H2RA .
3. Patients without risk factors do not receive prophylaxis.

Q. Nutrition:

1. Administer oral or enteral (if necessary) feedings, as tolerated, rather than either complete fasting or provision of onlyintravenous glucose within the first 48 hours after a diagnosis of severe sepsis/septic shock .

2. Avoid mandatory full caloric feeding in the first week but rather suggest low dose feeding (eg, up to 500 calories per day),advancing only as tolerated .
3. Use intravenous glucose and enteral nutrition rather than total parenteral nutrition (TPN) alone or parenteral nutrition inconjunction with enteral feeding in the first 7 days after a diagnosis of severe sepsis/septic shock .
4. Use nutrition with no specific immunomodulating supplementation rather than nutrition providing specific immunomodulatingsupplementation in patients with severe sepsis .

R. Setting Goals of Care:

1. Discuss goals of care and prognosis with patients and families.
2. Incorporate goals of care into treatment and end-of-life care planning, utilizing palliative care principles where appropriate.
3. Address goals of care as early as feasible, but no later than within 72 hours of ICU admission.[65]

HISTORY OF LACTATE:

Lactic acid or lactate, as its name implies,was first isolated from sour milk in the 18th century. In 1918, scientists observed cases in which metabolic acidosis was associated with decreased blood flow and shock. In the 1970's and 80's, the seminal works of Huckabee and Cohenfinally described the clinical syndrome of lactic acidosis as we know it today[68,69]. The clinical and physiologic condition of metabolic acidosis has been recognized for nearly a century, yet we are only now discovering new approaches for its diagnosis and treatment.

LACTIC ACIDOSIS:

Lactic acidosis indicates a severe metabolic derangement, with significant associated mortality. The term "lactic acidosis" actually embodies two separate pathologic processes: hyperlactatemia and metabolic acidemia. Because the most common cause of hyperlactatemia,cellular hypoxia, may simultaneously cause acidemia, the combined term lactic acidosis is commonly used to describe any condition of increased lactate levels. Despite this usage, many causes of hyperlactatemia are not associated with acidemia.

The traditional classification scheme of Cohen and Woods, which categorizes lacticacidoses as Type A (evidence of tissue hypoxia) and Type B (no evidence of tissuehypoxia) is still useful. The most common cause is inadequate tissueoxygen delivery, either global (shock) or compartmental (e.g. extremity or mesentericischemia). Anemia itself rarely causes lactic acidosis, unless the anemia is unusuallysevere. More commonly, anemia exacerbates cellular hypoxia caused by perfusion deficits by further impairing oxygen delivery.

Sepsis is associated with down-regulation of PDH activity and can cause parallelincreases in pyruvate and lactate levels. If sepsis is complicated by regional or globalhypoperfusion, acidosis with further increases in lactate and an increased lactate/pyruvateratio may occur[70]. A large number of drugs and toxins can cause elevated serum lactateconcentrations as a consequence of their metabolism, their effects on glucose metabolismor liver injury. The metabolism of large quantities of short-chain alcohols may consumeintermediates (NAD+) necessary for pyruvate utilization and produce an expansion ofthe pyruvate pool. Ethylene glycol and propylene glycol may be converted directly tolactate without pyruvate intermediates; ethylene glycol also causes acidemia throughthe production of glyoxylic and oxalic acids. Propylene glycol is a vehicle for certainwater-insoluble drugs such as lorazepam. If administered in sufficiently high doses,particularly in a patient with preexisting liver disease, it can cause hyperlactatemia[71,72].

Etiologies of Lactic Acidosis:

Type A (tissue hypoxia present):

- Shock (cardiogenic, hypovolemic, septic)
- Regional ischemia (extremity, mesenteric)
- Severe hypoxemia
- Severe anemia
- Asthma exacerbation
- Carbon monoxide poisoning
- Cyanide poisoning (including cyanide toxicity in nitroprusside therapy)
- Generalized seizures
- Congenital disorders of oxidative phosphorylation

Type B (no evidence of tissue hypoxia):

- Sepsis with no evidence of inadequate tissue oxygen delivery
- Drugs and toxins:
- Acetaminophen overdose
- Antiretroviral therapy of HIV
- Biguanides (metformin, phenformin)
- Ethanol or methanol intoxication
- Ethylene glycol poisoning
- Propylene glycol (drug vehicle) in large quantities
- Fructose (in large quantities)
- Isoniazid
- Salicylate overdose
- Various sugar alcohols, e.g., sorbitol, xylitol
- Severe deficiencies of thiamine or biotin
- Fulminant liver failure
- Diabetic ketoacidosis
- Hematologic malignancies and metastatic small cell carcinoma
- Short bowel or blind intestinal loop syndrome (D-lactic acidemia)
- Inborn errors of metabolism:
- Glucose-6-phosphatase deficiency
- Fructose-1,6-diphosphatase deficiency
- Pyruvate carboxylase deficiency
- Pyruvate dehydrogenase deficiency

An emerging etiology is antiretroviral therapy (ART) for HIV with nucleoside analog reverse transcriptase inhibitors such as zidovudine. These agents have been shown to cause mitochondrial dysfunction along with clinical manifestation of myopathy,neuropathy, myelotoxicity and possibly liver injury associated with lactic acidosis and an elevated lactate/pyruvate ratio[73].

Measurement of the lactate/pyruvate ratio has been advocated to monitor patients for ART-related toxicity [74]. Lactic acidosis also has been reported in HIV patients not receiving ART. Carnitine has been proposed as a possible treatment, because it acts as an acceptor for acyl groups from acyl CoA thus increasing the concentration of free CoA, which in turn stimulates the PDH complex [75]. Case reports have described decreases in serum lactate concentrations with carnitine administration but no prospective trials have evaluated the impact on survival [76].

Vitamin deficiencies are usually exacerbating factors in stressed patients with othercauses of hyperlactatemia. Thiamine is a necessary cofactor for PDH; biotin is necessary for pyruvate carboxylase which catalyzes the first step in gluconeogenesis from pyruvate. Hyperlactatemia also is associated with certainhematologic and solid tissue malignancies, especially small cell carcinoma with extensivehepatic metastases.

The large burden of tumor cells producing lactate is responsible[77.]Hepatic insufficiency rarely causes hyperlactatemia in unstressed patients unless veryprofound hepatic failure is present. However, it will prolong the half-life of a lactateload produced during a metabolic insult particularly if accompanied by hypoxia, acidosis,or splanchnic hypoperfusion which can further impair hepatic clearance. In general, lacticacidosis in a patient with liver disease has the same clinical significance as in a patient with normal liver function[78].

PATHOGENESIS OF LACTIC ACIDOSIS:

Hyperlactatemia:Lactate is a metabolic “dead end,” as it is derived exclusively from pyruvate (a rare exception will be noted later) and must be converted back to pyruvate to be utilized.

Lactate and pyruvate exist in a cytosolic equilibrium catalyzed by lactate dehydrogenase(LDH) and regulated by the concentrations of reactants and products

:Pyruvate + NADH+H^+----------Lactate + NAD^+

Lactate concentration thus depends on (1) NADH/NAD+ ratio and (2) pyruvate concentrations.Basal lactate production averages 20 mmol/kg per day (1400 mmol/day at70 kg)[79]. Normal plasma lactate concentrations are 1–2 mmol/L and the normallactate/pyruvate ratio is approximately 10–20 : 1.

Impairment of oxidative phosphorylation, by cellular hypoxia or other causesof mitochondrial dysfunction, causes the NADH/NAD+ ratio to rise. The lactate/pyruvateequilibrium is shifted toward lactate and the lactate concentration rises. Reduction ofpyruvate to lactate during cellular hypoxia actually may be useful, because it producesNAD+, which is necessary for ongoing glycolysis. The NADH/NAD+ ratio also maybe increased by the reduction of NAD+ to NADH during the metabolism of large amounts of other substrates such as ethanol. Mechanisms such as these cause hyperlactatemiawith an elevated lactate/pyruvate ratio (normal ¼ 10–20 : 1).

Effect of Pyruvate:

Increased pyruvate concentrations may result in increased lactate production. Pyruvateconcentrations in turn reflect relative rates of utilization and production.Pyruvate may be used for gluconeogenesis or may be oxidized to acetyl CoA by thepyruvate dehydrogenase complex (PDH). Acetyl CoA may undergo further oxidation

in the tricarboxylic acid (TCA) cycle or be used for the biosynthesis of fatty acids, cholesteroland other substances. Sepsis specifically inhibits PDH, thereby interfering withcellular energy production and pyruvate utilization [69].

The principal disposal route forpyruvate under this circumstance of down-regulation of PDH is gluconeogenesis via theCori cycle, which occurs in the liver and kidney only. When inhibition of PDH directsaccumulating pyruvate to gluconeogenesis, glycolysis returns the three carbon moieties back to the expanding pyruvate pool for eventual repeated gluconeogenesis (futilecycling) and further lactate buildup.

Pyruvate overproduction is a minor contributor to hyperlactatemia. The principalsources of pyruvate are glycolysis and deamination of gluconeogenic amino acids(especially alanine). Glycolysis may be accelerated by hypoxia, because a falling ATP/ADP, AMP ratio stimulates phosphofructokinase. Hypoxia also stimulates glycogenolysisby rapidly activating glycogen phosphorylase, the activity of which provides increasedsubstrate for glycolysis. Alkalosis stimulates glycolysis at the phosphofructokinase level,but its effect on lactate production may be partially offset by a shift in the lactate/pyruvateequilibrium toward pyruvate.

Sepsis and hypermetabolism drive protein catabolism withmobilization of large quantities of gluconeogenic amino acids, which ultimately contribute to the

pyruvate pool. Mechanisms such as these cause hyperlactatemia with anormal lactate/pyruvate ratio (normal ¼ 10–20:1).

Clearance of Lactate:

Normally, the liver clears up to 70% of a lactate load (largely through gluconeogenesis)and the kidneys clear 20–30% (via gluconeogenesis and oxidation). Hepatic extractionfollows saturable, second order kinetics, with a Vmax equal to 5.72 mmol/kg0.75 per hr(3300 mol/day at 70 kg).Hepatic dysfunction from acidosis, ischemia, hypoxia or underlying parenchymaldisease can markedly impair extraction. Renal excretion is minimal with a tubulartransport maximumof 6–10 mmol/L. Other tissues, such as skeletal and cardiac muscle can also utilize lactate (1).Associated Acidemia The principal endogenous source of H+ is ATP hydrolysis:

$$ATP + H_2O \rightarrow ADP + P_i + H^+$$

This H^+ is not consumed during the reverse reaction, ADP phosphorylation to ATP. Instead, this H^+ is eliminated in the final step of mitochondrial electron transport:

$$2H^+ + 2e^- + \frac{1}{2}O_2 \rightarrow H_2O$$

Impaired electron transport function, as a result of cellular hypoxia or cytochrome antagonists such as cyanide, interferes with this clearance of H+ and acidemia results.When excess lactate is produced from cellular hypoxia or other causes of mitochondrialdysfunctionacidemiaoccurs as well and true lactic acidosis. Note that endogenously produced lactate is the weak conjugate base of lactic acid; lactic acid is notproduced and is not the source of the acidemia in so-called lactic acidosis. Thus, hyperlactatemia may be accompanied by acidemia when the underlying etiology is mitchondrial dysfunction and will not be accompanied by

acidemia (unless another acid/base disturbance is present) when the etiology is pyruvate overproduction or impaired pyruvate utilization.

CLINICAL CORRELATES:

Lactic acidosis has been associated with weakness, malaise, anorexia, vomiting, changesin mental status, hyperventilation, tachycardia, hemodynamic instability, mildhypochloremia, hyperphosphatemia and hyperuricemia. Some data also support an independent deleterious effect of lactate as a negative inotrope [80,81]. In general, the manifestations of lactic acidosis are those of the underlying disorder[79].A correlation exists between the magnitude of lactic acidosis and the prognosis. The rate and magnitude of response to therapy and the etiology of the lacticacidosis are probably better indicators of prognosis and adequacy of treatment.If pyruvate determinations are available, thelactate/pyruvate ratio may be indicativeof the predominant class of derangement. A normal ratio [82] is associated withsepsis and certain metabolic disorders. An elevated ratio is consistent with hypoperfusion, hypoxemia, compartmental ischemia or interference withmitochondrial oxidation. Mixed disorders may occur.

TREATMENT:

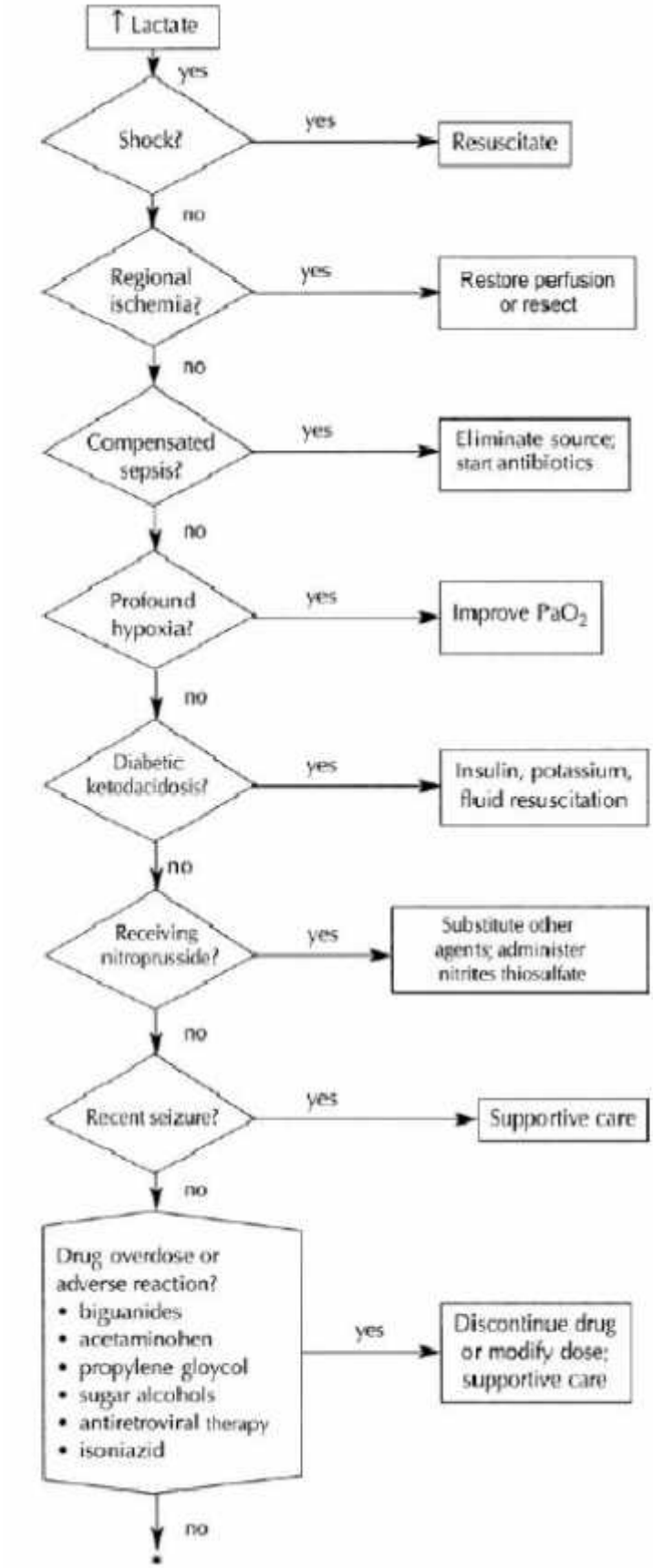
As hyperlactatemia, with or without metabolic acidemia, is a consequence of a severeunderlying metabolic disorder and not an independent disease state, treatment shouldbe directed at identifying and correcting the underlying disorder. As this disorderimproves, the lactic acidosis will resolve. Specific therapy and general supportive carewill be dictated by the patient's diagnosis and general condition.

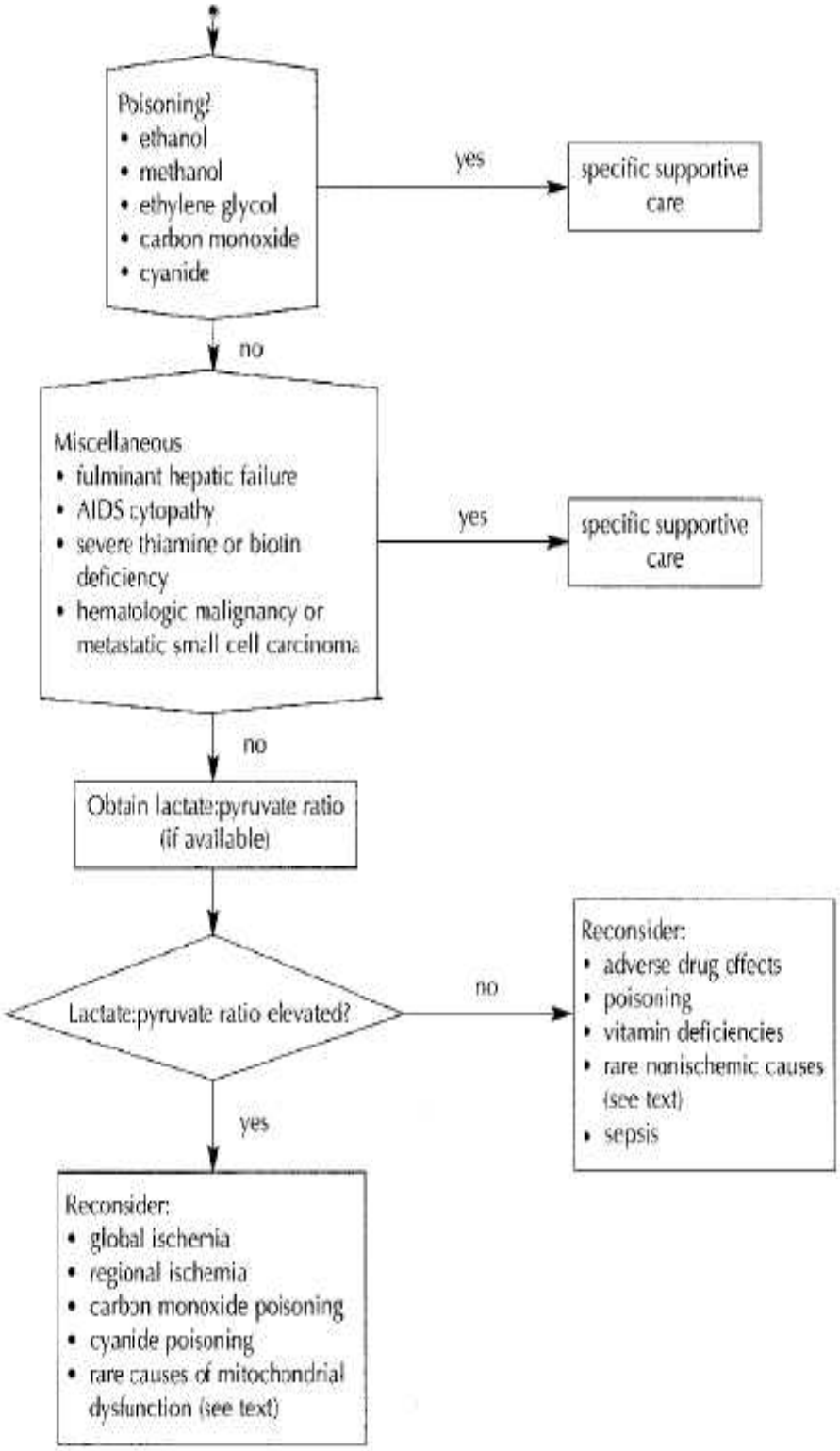
Inadequate tissue oxygen delivery should be corrected by improving cardiac performance,blood oxygen content and regional perfusion. Compartmental ischemia

(extremity or splanchnic) may require restoration of arterial or venous patency or resection. If sepsis is suspected, it should be treated by elimination of the infectious source, administration of antibiotics and restoration of adequate tissue oxygen delivery. The presence of toxins should be considered and excluded. Preexisting metabolic disorders, such as diabetes mellitus or thiamine deficiency, should be addressed.

Signs of resolving hyperlactatemia and acidemia indicate metabolic improvement,but occult hypoperfusion can still exist in the face of a normal or near-normal lactateconcentration. Acidemia in particular is a late consequence of tissue hypoxia. The principlesof establishment of flow-independent oxygen consumption should be considered.

Figure-8


↑ Lactate
yes
Shock?
yes
Resuscitate
no
Regional ischemia?
yes
Restore perfusion or resect
no
Compensated sepsis?
yes
Eliminate source; start antibiotics
no
Profound hypoxia?
yes
Improve PaO_2
no
Diabetic ketodacidosis?
yes
Insulin, potassium, fluid resuscitation
no
Receiving nitroprusside?
yes
Substitute other agents; administer nitrites thiosulfate
no
Recent seizure?
yes
Supportive care
no
Drug overdose or adverse reaction?
• biguanides
• acetaminohen
• propylene gloycol
• sugar alcohols
• antiretroviral therapy
• isoniazid
yes
Discontinue drug or modify dose; supportive care
no



ALGORITHM FOR DETERMINATION OF ETIOLOGY OF ELEVATED SERUM LACTATE

The management of severe metabolic acidemia is controversial. The basic strategyalways should be correction of the underlying derangement and restoration of adequateperfusion. A growing body of evidence suggests that alkali therapy (bicarbonate) isdeleterious, as it causes intracellular acidosis with paradoxical worsening of hyperlactatemia,a shift in the oxyhemoglobin dissociation curve to the left with impairment oftissue oxygenation, increased susceptibility to cardiac dysrhythmias and in patientswith congestive heart failure, sodium and fluid overload. Clinical evidence indicatesthat even severe acidemia (pH - 7.2) does not significantly affect hemodynamics, nordoes bicarbonate administration result in improvement[82]. Hemodialysis or peritonealdialysis may be useful in severe lactic acidosis associated with renal insufficiency or congestiveheart failure.Dichloroacetic acid (DCA) stimulates PDH activity and can lowerblood lactate concentration, but in a randomized trial failed to improve survival .

MATERIALS AND METHODS

SOURCE OF DATA:

- All patients admitted to B.L.D.E.U. s Shri B M Patil Medical College, Hospital and Research Centre and admitted with sepsis.
- Study period from: October 2014 to June 2016

METHOD OF COLLECTION OF DATA:

- Patients admitted with sepsis condition in B.L.D.E.U s Shri. B.M. Patil Medical College, Hospital and Research Centre, Vijayapur from October 2014 to June 2016.
- History of patients was noted.
- Required basic investigations were done.
- Serum lactate investigation was done at the time of admission and after 24-48 hrs after admission.

INCLUSION CRITERIA:

All patients admitted in B.L.D.E.U's Shri B.M Patil Medical College, Hospital and Research Centre, Vijayapurwith diagnosis of sepsis satisfying the inclusion and exclusion criteria were taken for the study.

Must be an adult (>18yrs)

Meet 2 or more criteria for systemic inflammatory response syndrome

i. Temperature >38*C or < 36*C (100.4*F/96.8*F)

ii. Pulse rate >90/min

iii. Respiratory rate >20/min or PaCO2 <32 mm Hg

iv. WBC count >12,000 cumm3 or <4000 cumm3 or >10% immature(bands).

Must have sepsis with any of these signs of hypoperfusion,

i. SBP<90 or >40mm Hg drop in standard BP even after adequate fluid resuscitation.
ii. Serum Creatinine> 2.0 mg/dl or Urine output <30ml//hour.
iii. Total Bilirubin >4mg/dl.
iv. Lactate >2.5 mMol/L.

EXCLUSION CRITERIA:

- Chronic liver disease
- End stage cardiopulmonary disease.
- Neoplasms.
- HIV positive cases with known end stage processes.

STUDY METHODS:

The present study was a prospective study.

The study period was from October-2014 to June -2016

- A total of 170 sepsis patients were taken for thestudy.
- All these patients were evaluated thoroughly by clinical, radiological andlaboratory methods.
- Serum lactate 1st and 2nd samples were collected.
- Serum lactate levels were categorized into
    1. Low positive (0-2.0Mol/L)
    2. Moderate positive(2.1-3.9mMol/L)
    3. Highly positive(>4mMol/l)

STATISTICAL METHODS :

Statistical analysis was performed using Chisquare test, student 't' test and Odd's ratio.

RESEARCH HYPOTHESIS:.

To estimate the serum lactate in patients with sepsis and to correlate the value with the clinical condition and to evaluate the outcome.

SAMPLING:

Study period from: October 2014 to June 2016.

All the patients admitted during this period, who fulfilled the inclusion criteria, were included in this study.

Sample size was calculating using the formula,

$$n = \frac{Z\sim^{2} p(1-p)}{d^{2}}$$

Where, n=sample size,

Zα=1.96 at 5% level of significance.

p= Prevalence rate= 20%

d= allowable error=±6%.

For present study it was planned to conduct study on 170 patients, as this study was a prospective type.

Following statistical tests were used to compare the results:

- Student t test.
- Chi-square test.
- Mean± Standard deviation.

INVESTIGATIONS / INTERVENTIONS:

Investigations or interventions required in this study were routine standardized procedures.

There were no animal experiments involved in this study.

Following investigations were needed for the study.

- Serum lactate levels at 0 and 24 hrs.
- Hb%, TC, DC, ESR, platelet count.
- Urea, creatinine& electrolytes.
- Urine routine.
- RBS

FOLLOWING INVESTIGATIONS (AS AND WHEN REQUIRED):

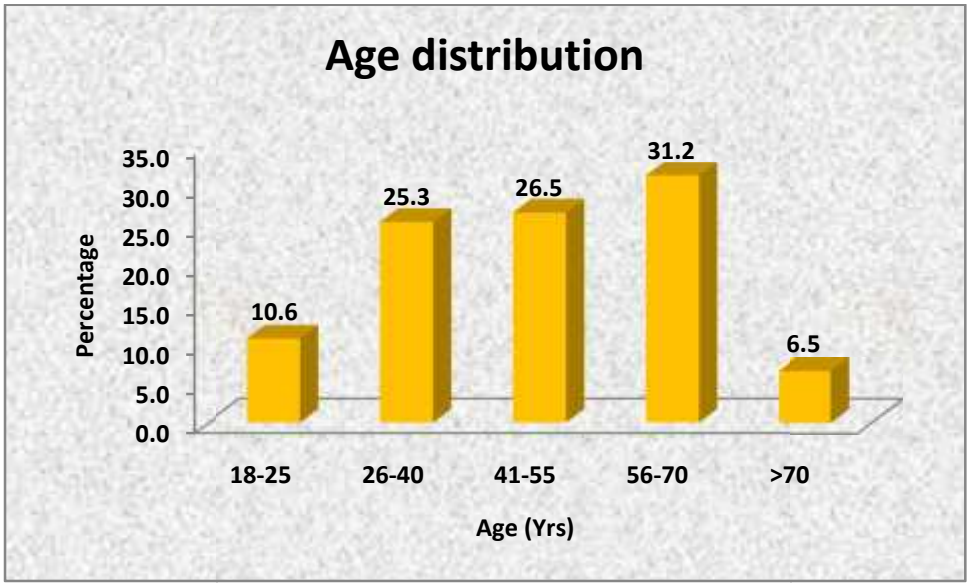
- ABG
- Chest X-ray
- Blood culture/Urine culture/Pus culture.
- USG Abdomen and Pelvis.
- LFT

RESULTS

Table 1: Distribution of cases according to Age (Yrs)

Age (Yrs)	Number	%
18-25	18	10.6
26-40	43	25.3
41-55	45	26.5
56-70	53	31.2
>70	11	6.5
Total	170	100.0

Figure-9: Graph showing Distribution of cases according to Age (Yrs)

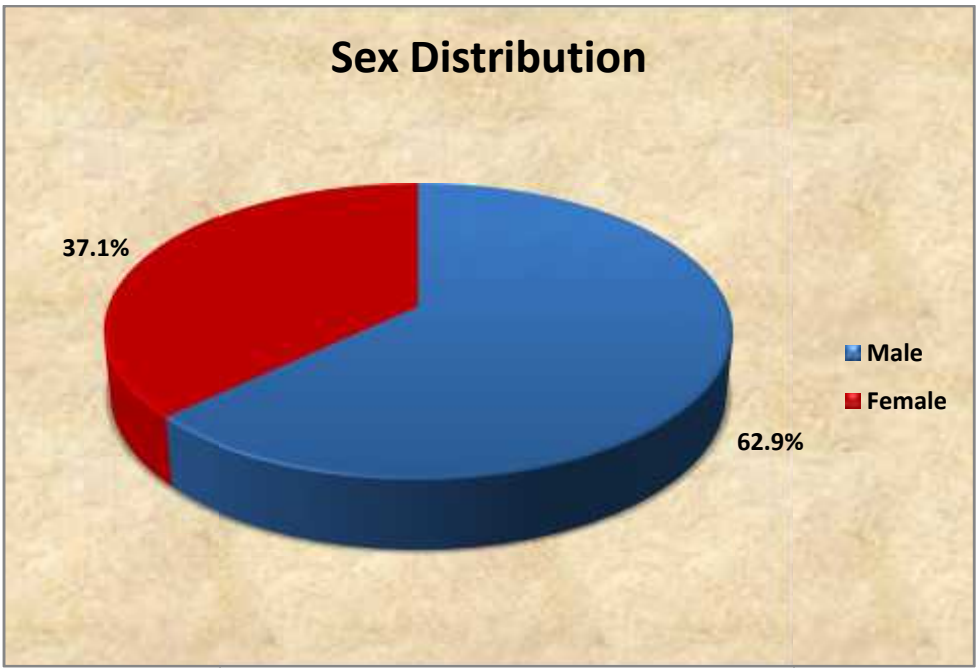


In present study it was observed that highest number of patients were observed in age group 56-70yrs, with mean age group of 31.2 yrs.

Table 2: Distribution of cases according to Sex

Sex	Number	%
Male	107	62.9
Female	63	37.1
Total	170	100.0

Figure-10: Graph showing Distribution of cases according to Sex

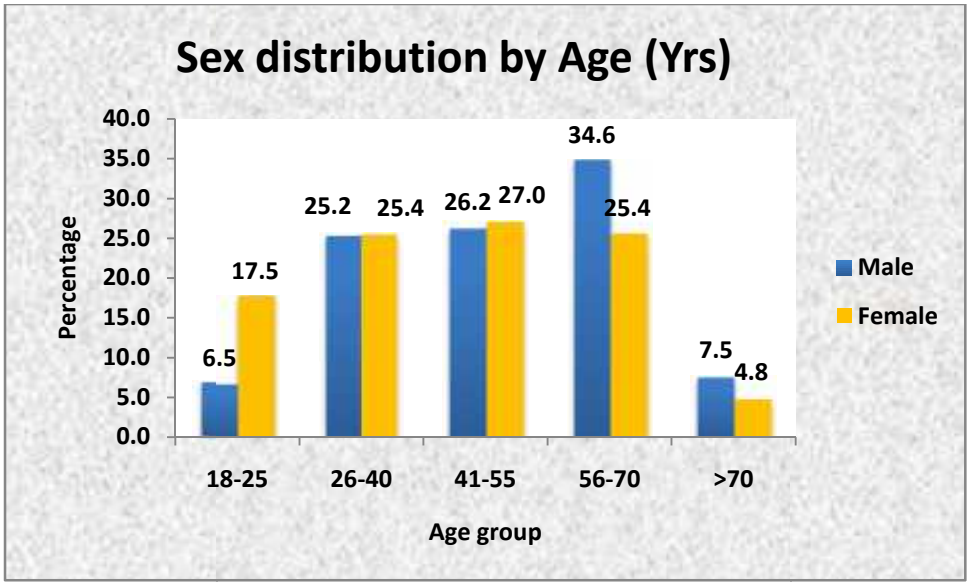


In present study it was observed that increased number of patients were seen in male gender with 62.9% of all patients.

Table 3: Distribution of cases according to Age (Yrs) & Sex

Age (Yrs)	Male		Female	
	N	%	N	%
18-25	7	6.5	11	17.5
26-40	27	25.2	16	25.4
41-55	28	26.2	17	27.0
56-70	37	34.6	16	25.4
>70	8	7.5	3	4.8
Total	107	100.0	63	100.0

FIGURE-11: GRAPH SHOWING DISTRIBUTION OF CASES ACCORDING TO AGE (YRS) & SEX

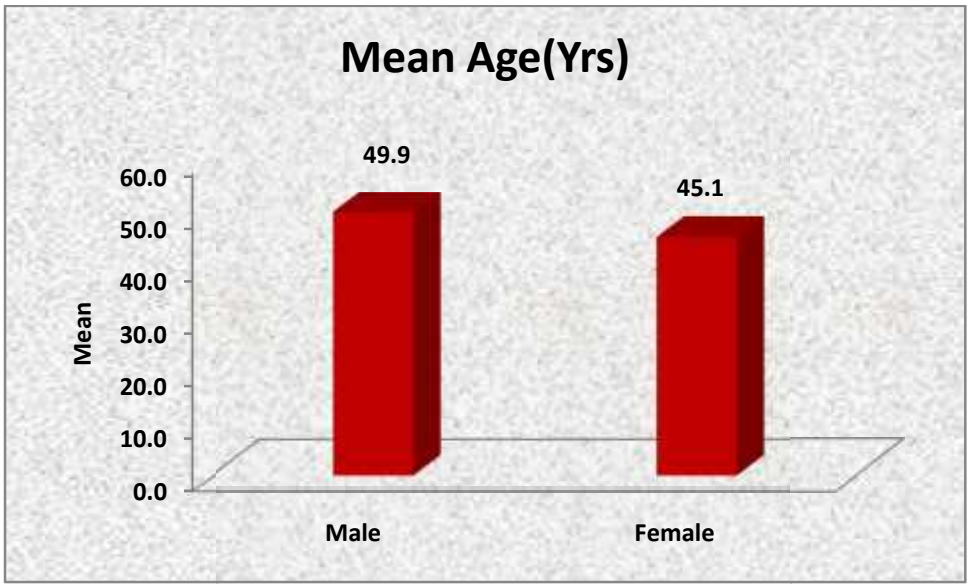


In present study it was observed that increased number of male patients were observed in age group 56-70 yrs and increased number of female patients were observed in age group 41-55 yrs.

TABLE 4: MEAN AGE BY SEX

Age (Yrs)	Male	Female	Total
Mean±SD	49.9±16.5	45.1±17.4	48.1±16.9

FIGURE-12: GRAPH SHOWING MEAN AGE BY SEX

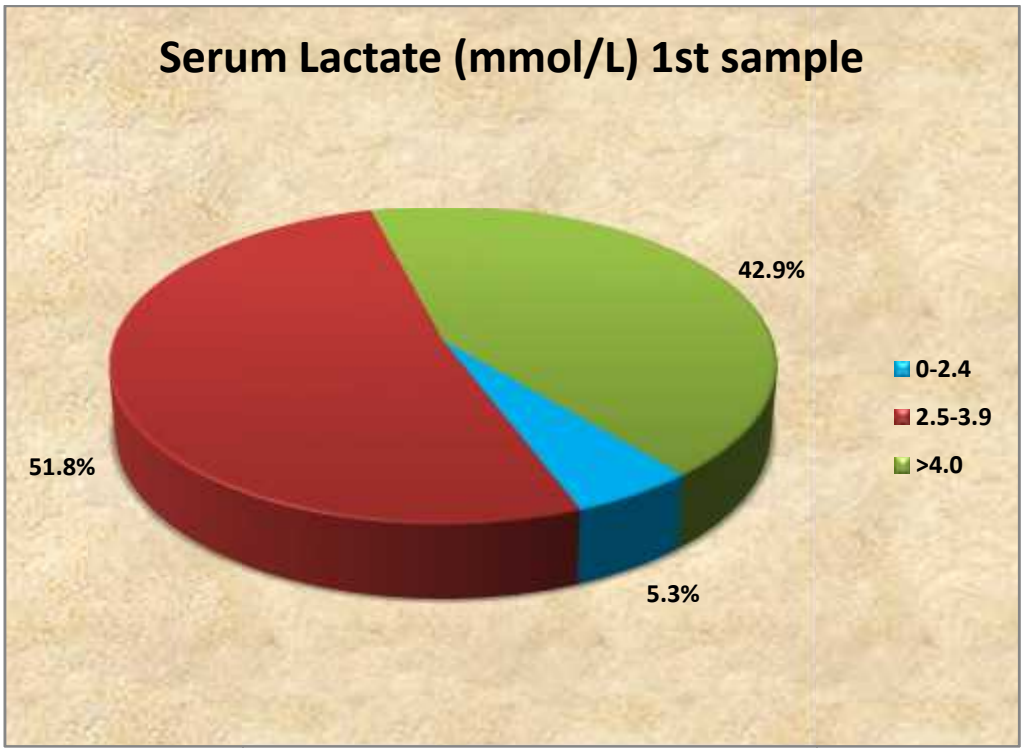


In present study it was observed that mean age of male patients was 49.9yrs±16.5 and female was 45.1±17.4.

Table 5: Distribution of cases according to Serum Lactate (mmol/L) 1st sample

Serum Lactate (mmol/L) 1st sample	N	%
0-2.4	9	5.3
2.5-3.9	88	51.8
>4.0	73	42.9
Total	170	100.0

Figure- 13: Graph showing Distribution of cases according to Serum Lactate (mmol/L) 1st sample

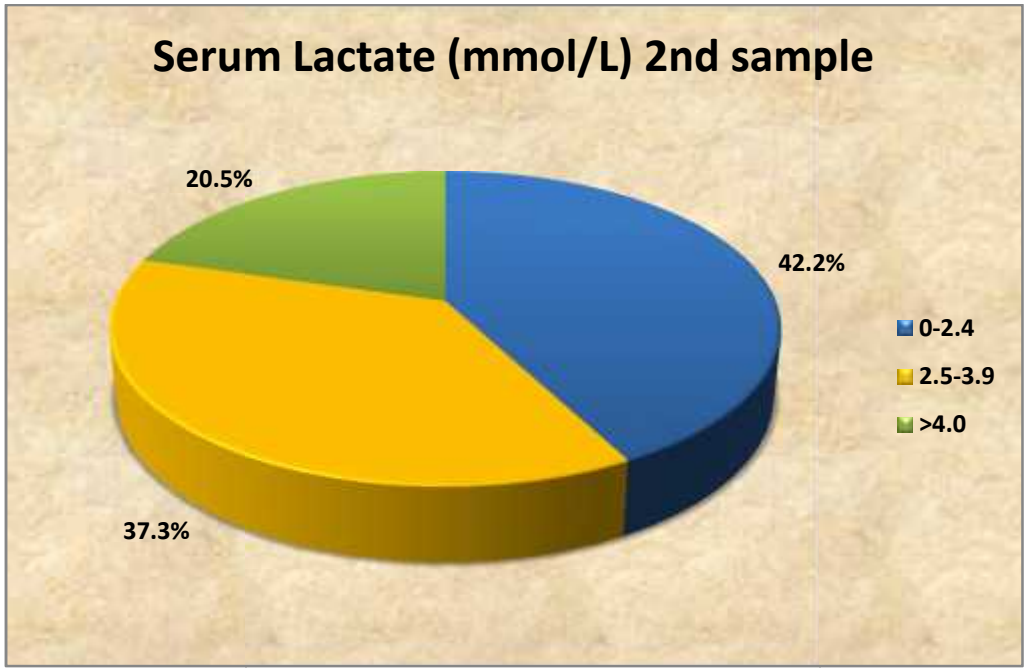


In present study it is observed that serum lactate 1st value in between 2.5-3.9 is more i.e 51.8% and serum lactate value >4.0 in 42.9% and serum lactate value 0-2.4 in 5.3%.

Table 6: Distribution of cases according to Serum Lactate (mmol/L) 2nd sample

Serum Lactate (mmol/L) 2nd sample	N	%
0-2.4	68	42.2
2.5-3.9	60	37.3
>4.0	33	20.5
Total	161	100.0

Figure-14: Distribution of cases according to Serum Lactate (mmol/L) 2nd sample

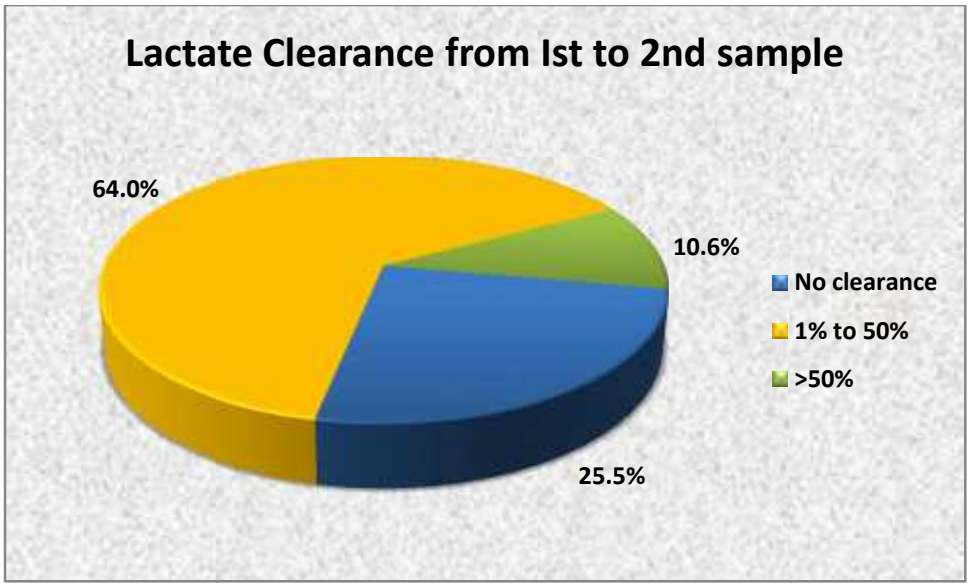


In present study it is observed that in 42.2% of the patients the serum lactate second sample value was found to be in between 0-2.4mmol/l.

TABLE -7 : DISTRIBUTION OF CASES ACCORDING TO LACTATE CLEARANCE FROM IST TO 2ND SAMPLE

Lactate clearance from Ist to 2nd sample	**N**	**%**
No clearance	41	25.4
1% to 50%	103	64.0
>50%	17	10.6
Total	161	100.0

FIGURE-15: GRAPH SHOWING DISTRIBUTION OF CASES ACCORDING TO LACTATE CLEARANCE FROM IST TO 2ND SAMPLE

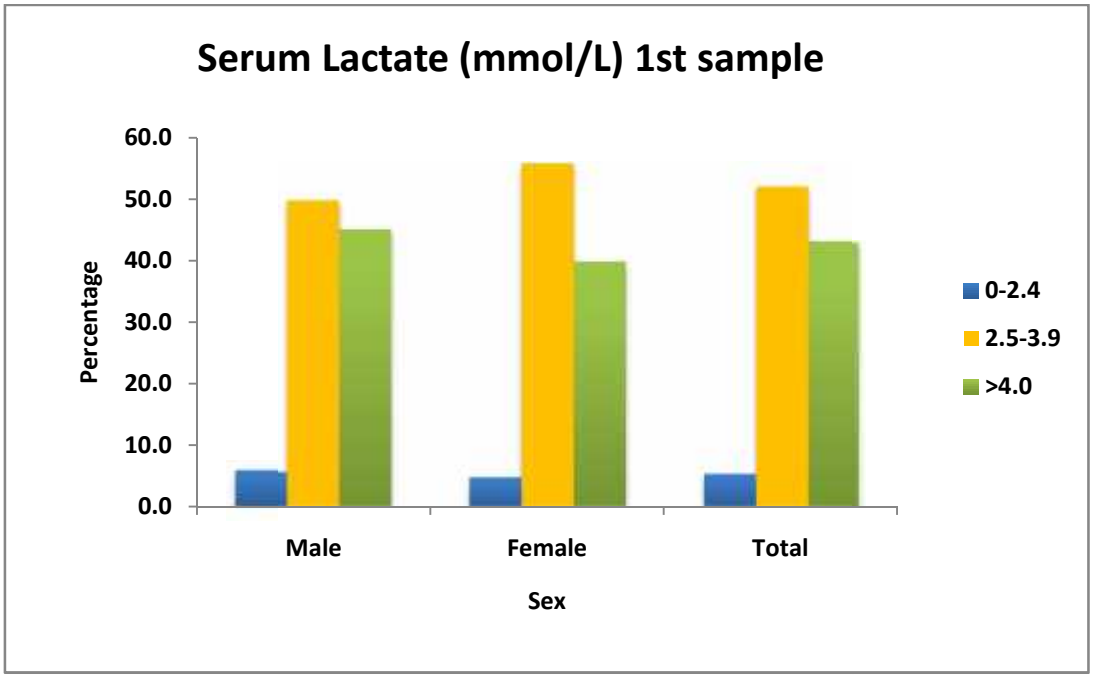


In present study it was observed that 103 patients showed lactate clearance from 1 to 50%(decrease in serum lactate values compared to 1st and 2nd) and 17 patients showed lactate clearance >50%.

Table-8 :Serum Lactate (mmol/L) 1st sample by Sex distribution

Serum Lactate (mmol/L) 1st sample	0-2.4		2.5-3.9		>4.0		Total	p value
Sex	**N**	**%**	**N**	**%**	**N**	**%**	**N**	
Male	6	5.6	53	49.5	48	44.9	107	0.749
Female	3	4.8	35	55.6	25	39.7	63	
Total	9	5.3	88	51.8	73	42.9	170	

Figure-16: Serum Lactate (mmol/L) 1st sample by Sex distribution

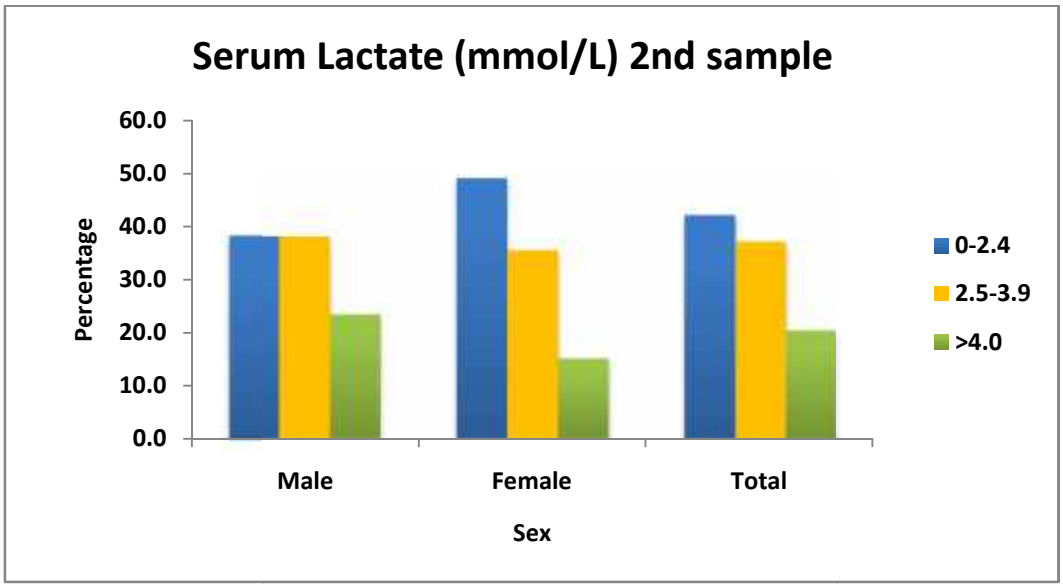


In present study it was observed that 53(49.5%) male patients presented with 1st sample serum lactate value in between 2.5-3.9 mmol/L and 48(44.9%) male patients presented with serum lactate value > 4.0 mmol/L.

Table-9 :Serum Lactate (mmol/L) 2nd sample by Sex distribution

Serum Lactate (mmol/L) 2nd sample	0-2.4		2.5-3.9		>4.0		Total	p value
Sex	**N**	**%**	**N**	**%**	**N**	**%**	**N**	
Male	39	38.2	39	38.2	24	23.5	102	0.305
Female	29	49.2	21	35.6	9	15.3	59	
Total	68	42.2	60	37.3	33	20.5	161	

Figure-17: Serum Lactate (mmol/L) 2nd sample by Sex distribution

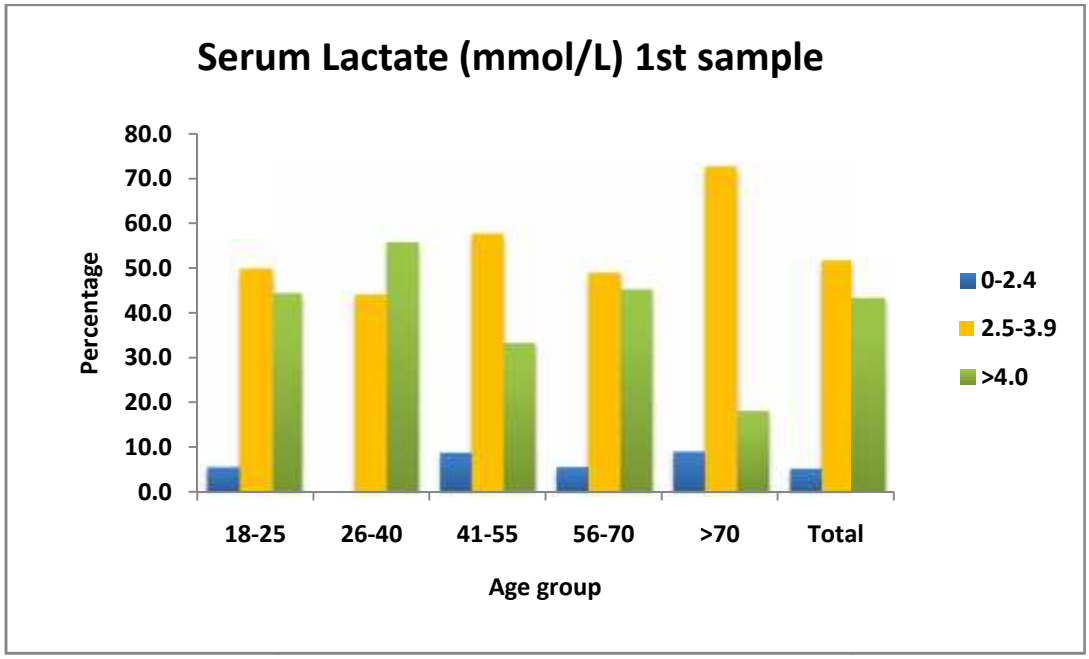


In present study it was observed that 39(38.2%) male patients presented with 2nd sample serum lactate value in between 2.5-3.9 mmol/L and 24(23.5%) male patients presented with serum lactate value > 4.0 mmol/L.

Table-10: Serum Lactate (mmol/L) 1st sample by Age (Yrs)

Serum Lactate (mmol/L) 1st sample	0-2.4		2.5-3.9		>4.0		Total	p value
Age (Yrs)	N	%	N	%	N	%	N	
18-25	1	5.6	9	50.0	8	44.4	18	0.281
26-40	0	0.0	19	44.2	24	55.8	43	
41-55	4	8.9	26	57.8	15	33.3	45	
56-70	3	5.7	26	49.1	24	45.3	53	
>70	1	9.1	8	72.7	2	18.2	11	
Total	9	5.3	88	51.8	73	42.9	170	

Figure-18: Serum Lactate (mmol/L) 1st sample by Age (Yrs)

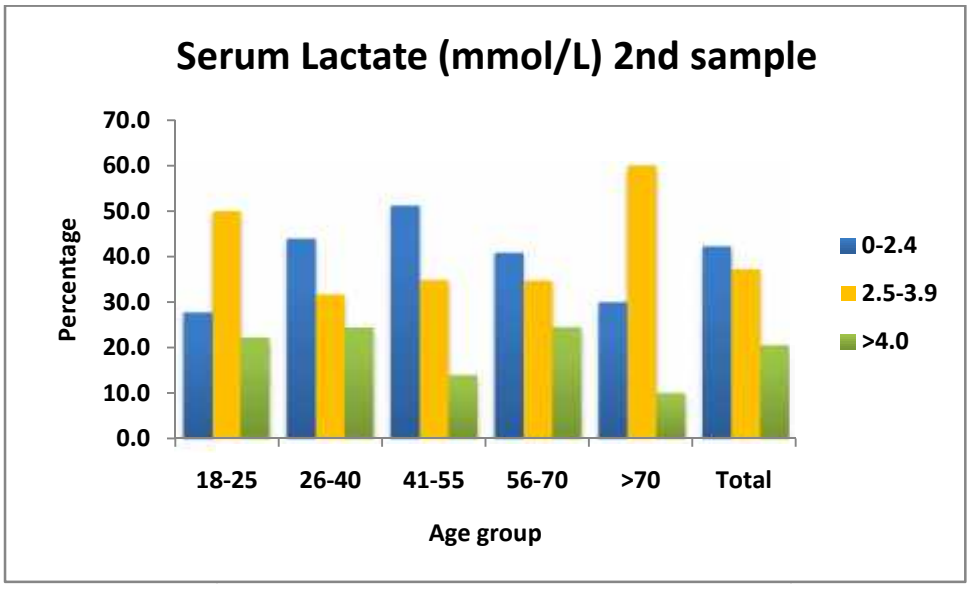


In present study it was observed that more number of patients who presented with sepsis were in the age group 56-70yrs with 1st sample of serum lactate value >4.0mmol/L.

Table -11: Serum Lactate (mmol/L) 2nd sample by Age (Yrs)

Serum Lactate (mmol/L) 2nd sample	0-2.4		2.5-3.9		>4.0		Total	p value
Age (Yrs)	N	%	N	%	N	%	N	
18-25	5	27.8	9	50.0	4	22.2	18	0.546
26-40	18	43.9	13	31.7	10	24.4	41	
41-55	22	51.2	15	34.9	6	14.0	43	
56-70	20	40.8	17	34.7	12	24.5	49	
>70	3	30.0	6	60.0	1	10.0	10	
Total	68	42.2	60	37.3	33	20.5	161	

Figure-19: Serum Lactate (mmol/L) 2nd sample by Age (Yrs)



In present study it was observed that more number of patients who presented with sepsis were in the age group 56-70yrs with 2nd sample of serum lactate value >4.0mmol/L.

Table-12: Distribution of Mean values of parameters by level of Serum Lactate (mmol/L) 1st sample

Parameters	Serum Lactate (mmol/L) 1st sample	N	Min	Max	Mean	SD	ANOVA p value
Age	0-2.4	9	22	82	53.1	18.1	0.584
	2.5-3.9	88	18	87	48.5	17.0	
	>4.0	73	18	80	47.1	16.7	
	Total	170	18	87	48.1	16.9	
PR	0-2.4	9	94	112	102.4	6.6	0.310
	2.5-3.9	88	82	116	99.6	6.3	
	>4.0	73	84	130	101.0	8.4	
	Total	170	82	130	100.4	7.3	
RR	0-2.4	9	20	28	23.6	2.8	0.225
	2.5-3.9	88	16	36	23.6	2.3	
	>4.0	73	20	34	24.3	2.4	
	Total	170	16	36	23.9	2.4	
SBP	0-2.4	9	80	154	100.7	26.7	0.504
	2.5-3.9	88	70	160	94.5	14.7	
	>4.0	73	80	150	96.1	16.0	
	Total	170	70	160	95.5	16.0	
DBP	0-2.4	9	50	88	63.1	12.5	0.794
	2.5-3.9	88	0	90	61.5	11.4	
	>4.0	73	46	90	62.6	10.5	
	Total	170	0	90	62.0	11.0	
TEMP	0-2.4	9	38	39.1	38.6	0.4	0.361
	2.5-3.9	88	34.4	39.6	38.4	0.9	
	>4.0	73	37	39.9	38.5	0.7	

	Total	170	34.4	39.9	38.5	0.8	
Total Count	0-2.4	9	12400	25900	17106.7	4699.9	0.688
	2.5-3.9	88	2300	40000	16910.7	5495.5	
	>4.0	73	2000	77100	17931.2	9567.2	
	Total	170	2000	77100	17359.3	7472.5	
Neutrophils	0-2.4	9	74	90	82.6	5.7	0.565
	2.5-3.9	88	69	95	84.2	6.5	
	>4.0	73	46	98	85.0	8.0	
	Total	170	46	98	84.4	7.2	
RBS	0-2.4	9	81	178	114.6	36.6	0.522
	2.5-3.9	88	63	504	140.9	72.4	
	>4.0	73	50	331	136.3	63.0	
	Total	170	50	504	137.5	67.0	
B.UREA	0-2.4	9	24	76	40.4	15.0	0.483
	2.5-3.9	88	14	370	55.9	46.2	
	>4.0	73	14	127	56.7	28.6	
	Total	170	14	370	55.4	38.3	
S.CREATININE	0-2.4	9	0.7	2.1	1.1	0.5	0.067
	2.5-3.9	88	0.4	5.4	1.6	1.0	
	>4.0	73	0.4	3.8	1.9	1.0	
	Total	170	0.4	5.4	1.7	1.0	

Table-13: Distribution of Mean values of parameters by level of Serum Lactate (mmol/L) 2nd sample

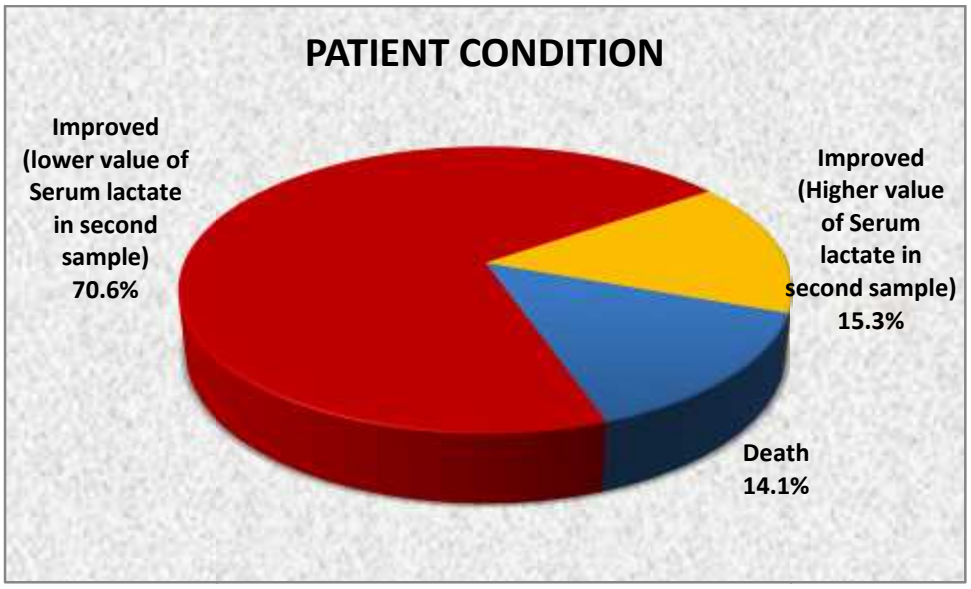
Parameters	Serum Lactate (mmol/L) 2nd sample	N	Min	Max	Mean	SD	ANOVA p value
Age	0-2.4	68	18	82	47.6	16.1	0.992
	2.5-3.9	60	18	87	48.0	18.1	
	>4.0	33	21	80	47.6	16.7	
	Total	161	18	87	47.8	16.9	
PR	0-2.4	68	82	116	98.4	6.3	0.000
	2.5-3.9	60	90	116	100.6	6.2	
	>4.0	33	92	130	104.4	9.6	
	Total	161	82	130	100.4	7.4	
RR	0-2.4	68	16	28	23.4	2.0	0.020
	2.5-3.9	60	20	30	24.0	1.9	
	>4.0	33	20	36	24.8	3.4	
	Total	161	16	36	23.9	2.4	
SBP	0-2.4	68	70	160	95.3	16.2	0.745
	2.5-3.9	60	80	150	96.8	16.7	
	>4.0	33	80	140	94.2	15.3	
	Total	161	70	160	95.6	16.1	
DBP	0-2.4	68	0	88	60.5	11.4	0.247
	2.5-3.9	60	50	90	63.8	11.0	
	>4.0	33	46	90	62.3	10.9	
	Total	161	0	90	62.1	11.2	
TEMP	0-2.4	68	34.4	39.6	38.4	1.0	0.406
	2.5-3.9	60	36	39.6	38.4	0.7	
	>4.0	33	37	39.9	38.6	0.7	

	Total	161	34.4	39.9	38.4	0.8	
Total Count	0-2.4	68	4800	28840	16915.0	4616.9	0.768
	2.5-3.9	60	2000	40000	17397.3	6402.1	
	>4.0	33	2890	77100	18088.5	12986.2	
	Total	161	2000	77100	17335.2	7613.3	
Neutrophils	0-2.4	68	69	97	84.8	6.6	0.910
	2.5-3.9	60	69	94	84.3	6.4	
	>4.0	33	46	98	84.4	10.0	
	Total	161	46	98	84.5	7.3	
RBS	0-2.4	68	70	442	133.8	63.2	0.637
	2.5-3.9	60	50	504	132.5	69.9	
	>4.0	33	55	301	145.4	66.4	
	Total	161	50	504	135.7	66.2	
B.UREA	0-2.4	68	14	370	54.5	47.2	0.462
	2.5-3.9	60	15	158	51.6	30.4	
	>4.0	33	18	125	62.0	32.3	
	Total	161	14	370	55.0	38.7	
S.CREATININE	0-2.4	68	0.4	5.4	1.5	0.9	0.006
	2.5-3.9	60	0.4	3.8	1.6	0.9	
	>4.0	33	0.7	5	2.1	1.0	
	Total	161	0.4	5.4	1.7	0.9	

TABLE-14: DISTRIBUTION OF PATIENT'S CONDITION

Patient Condition	N	%
Death	24	14.1
Improved (lower value of Serum lactate in second sample)	120	70.6
Improved (Higher value of Serum lactate in second sample)	26	15.3
Total	170	100.0

FIGURE-20: DISTRIBUTION OF PATIENT'S CONDITION



Number of patients who recovered with decrease in the serum lactate value(compared to 1st and 2nd sample)-**120**(70.6%)

Number of patients who recovered with increase in serum lactate values(compared to 1st and 2nd sample)- **26**(15.3%)

Number of patients who died because of septic shock and associated comorbidities with significant increase in serum lactate values(serum lactate values > 4 in both 1st and 2nd sample- **16** (9.41%)

Number of patients who died within 2 days of admission with significant 1st sample serum lactate value(serum lactate value >4) – **8** (4.7%)

TABLE-15: DISTRIBUTION OF CASES BY SOURCE OF INFECTION

Source of infection	N	%
Abdominal surgeries	46	27.2
Abscess	36	21.0
Necrotisingfascitis	36	21.0
Cellulitis	35	20.0
Burns	14	8.2
Urinary infection	3	1.8
Total	170	100.0

TABLE-16: MEAN PARAMETERS OF PATIENTS (N=170)

Parameters	Mean	SD	Range
Age (Yrs)	48.1	16.9	18-87
Serum Lactate (mmol/L) Ist sample	4.1	1.6	1.8-10.8
Serum Lactate (mmol/L) 2nd sample	3.1	1.6	0.8-11.1
PR	100.4	7.3	82-130
RR	23.9	2.4	16-36
SBP	95.5	16.0	70-160
DBP	62.0	11.0	0-90
Temp	38.5	0.8	34.4-39.9
Total Count	17359.3	7472.5	2000-77100
Neutrophils	84.4	7.2	46-98
RBS	137.5	67.0	50-504
B.Urea	55.4	38.3	14-370
S.Creatinine	1.7	1.0	0.4-5.4

TABLE-17: COMPARISON OF MEAN SERUM LACTATE BY SURVIVAL

Parameters	Survivors (N=146)		Non-survivors (N=24)		p value
	Mean	SD	Mean	SD	
Serum Lactate (mmol/L) Ist sample	3.8	1.2	6.2	1.9	<0.001 (Sig)

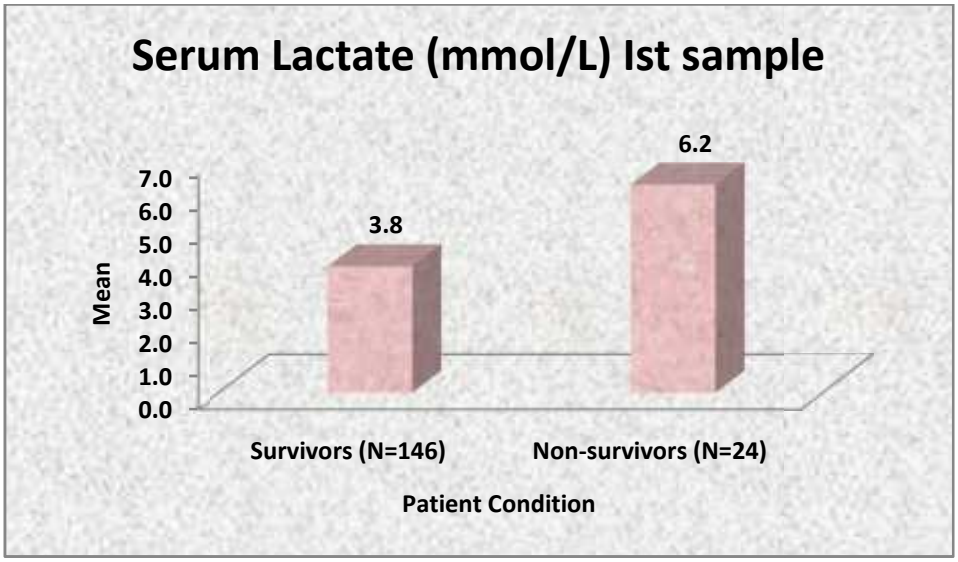


FIGURE-21 GRAPH SHOWING SERUM LACTATE 1ST MEAN VALUE IN SURVIVORS AND NON SURVIVORS

In present study it was observed that serum lactate mean value of 1st sample in survivors was 3.8mmol/L and in non survivors was 6.2 mmol/L.

COMPARISON OF MEAN SERUM LACTATE BY SURVIVAL

Parameters	Survivors (N=146)		Non-survivors (N=16)		p value
	Mean	SD	Mean	SD	
Serum Lactate (mmol/L) 2nd sample	2.7	1.0	6.3	1.8	<0.001 (Sig)

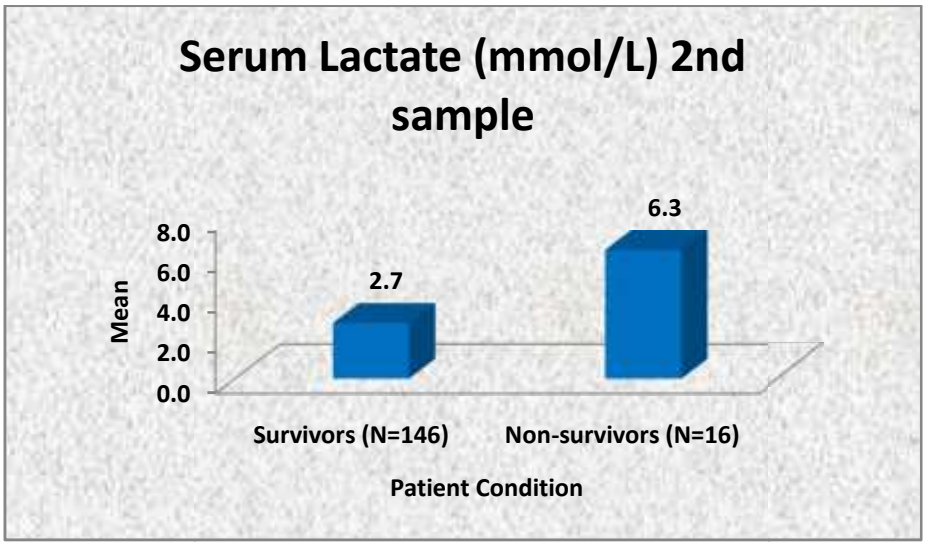


FIGURE-22 GRAPH SHOWING SERUM LACTATE SECOND SAMPLE MEAN VALUE IN SURVIVORS AND NON SURVIVORS

In present study it was observed that serum lactate mean value of 2nd sample in survivors was 2.7mmol/L and in non survivors was 6.3 mmol/L.

TABLE-18: COMPARISON OF MEAN PARAMETERS BY SURVIVAL

Parameters	Survivors (N=146)		Non-survivors (N=24)		p value
	Mean	SD	Mean	SD	
Age (Yrs)	47.6	16.9	51.5	17.2	0.292
PR	99.6	6.6	105.2	9.6	<0.001 (Sig)
RR	23.8	2.4	24.5	1.9	0.180
SBP	95.6	16.0	94.7	16.4	0.782
DBP	62.4	11.3	60.0	9.0	0.328
Temp	38.4	0.8	38.6	0.6	0.234
Total Count	16978.0	5327.3	19678.8	14994.4	0.101
Neutrophils	84.3	6.7	85.0	9.7	0.675
RBS	137.1	66.8	140.4	69.6	0.824
B.Urea	54.7	39.5	60.2	30.8	0.516
S.Creatinine	1.6	1.0	2.1	1.0	0.019 (Sig)

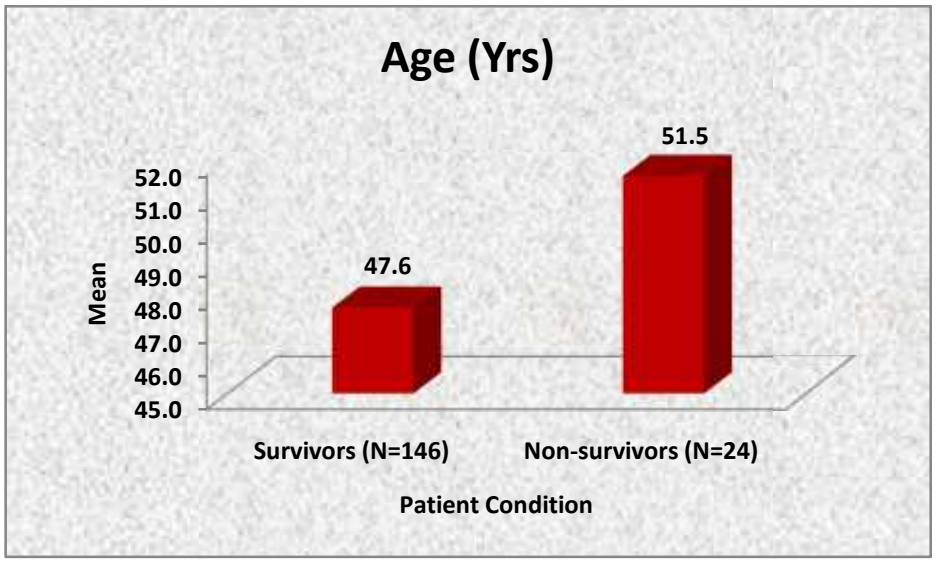


FIGURE-23 GRAPH SHOWINGMEAN AGE IN SURVIVORS AND NON SURVIVORS

In present study it was observed that mean age was 47.6 in survivors and 51.5 in non survivors.

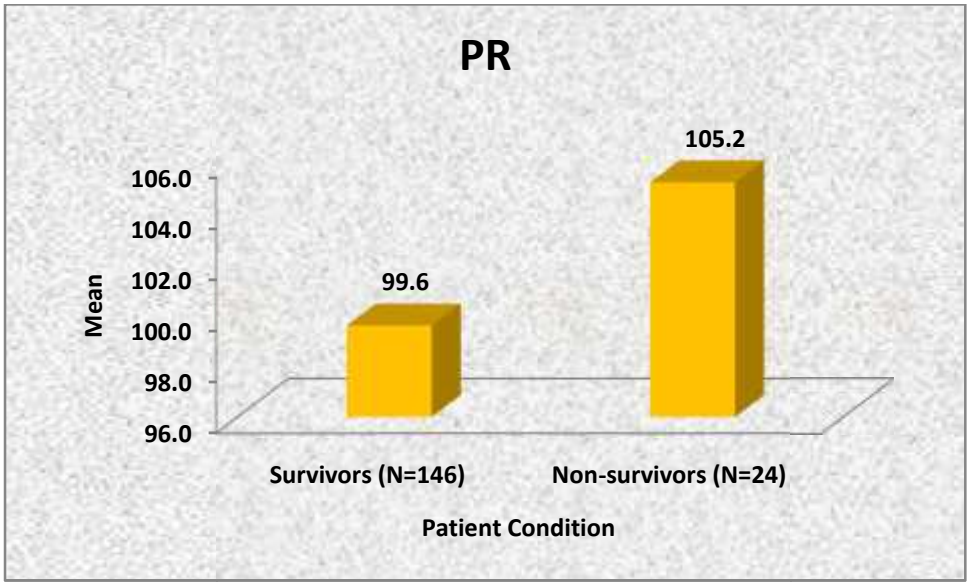


FIGURE-24 GRAPH SHOWING MEANPULSE RATE IN SURVIVORS AND NON SURVIVORS

In present study it was observed that mean pulse rate was 99.6 in survivors and 105.2 in non survivors.

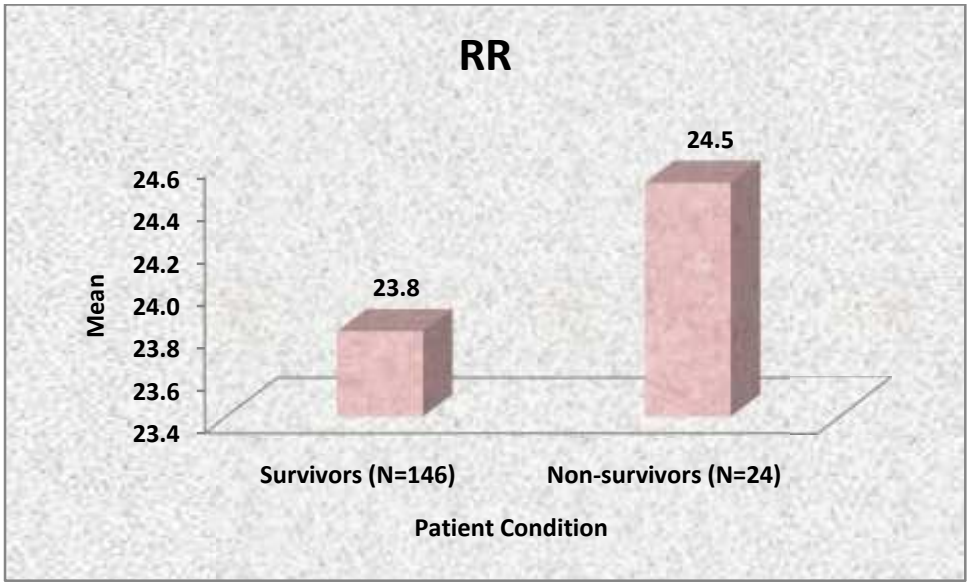


FIGURE-25 GRAPH SHOWING MEAN RESPIRATORY RATE BETWEEN SURVIVORS AND NON SURVIVORS

In present study it was observed that mean respiratory rate was 23.8 in survivors and 24.5 in non survivors.

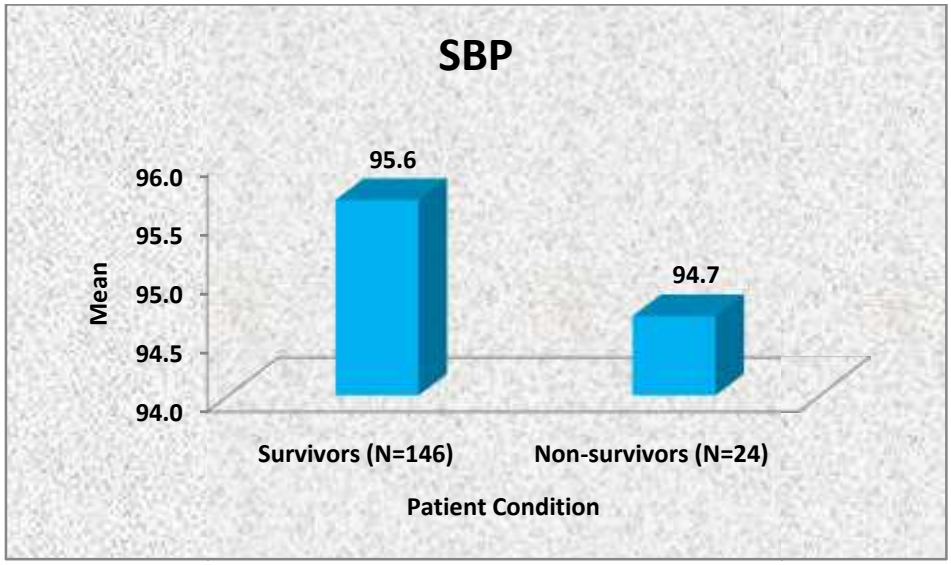


FIGURE-26 GRAPH SHOWING MEANSYSTOLIC BLOOD PRESSURE IN SURVIVORS AND NON SURVIVORS

In present study it was observed that mean systolic blood pressure was 95.6 in survivors and 94.7 in non survivors.

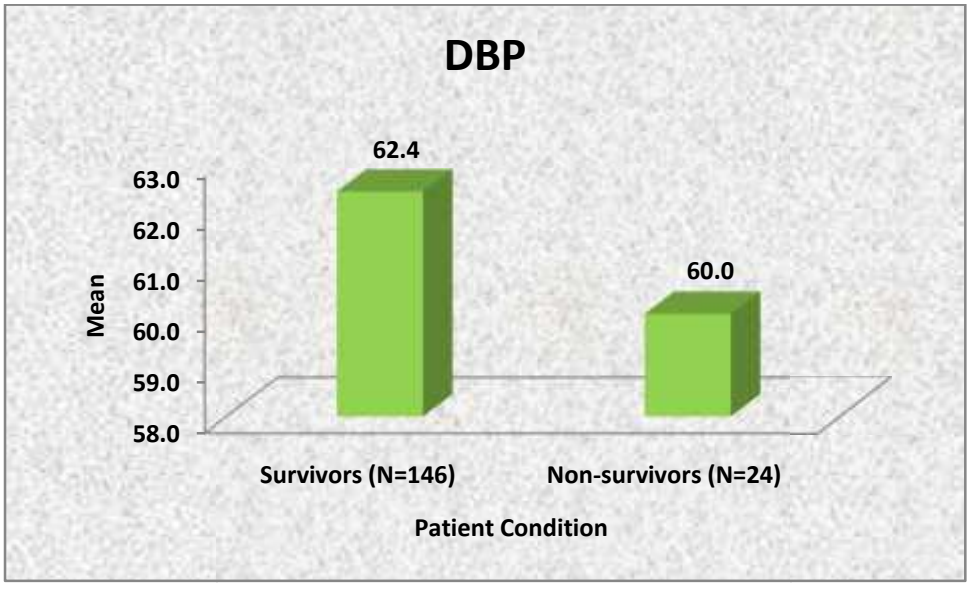


FIGURE-27 GRAPH SHOWING MEAN DIASTOLIC BLOOD PRESSURE IN SURVIVORS AND NONSURVIVORS

In present study it was observed that mean diastolic blood pressure was 62.4 in survivors and 60 in non survivors.

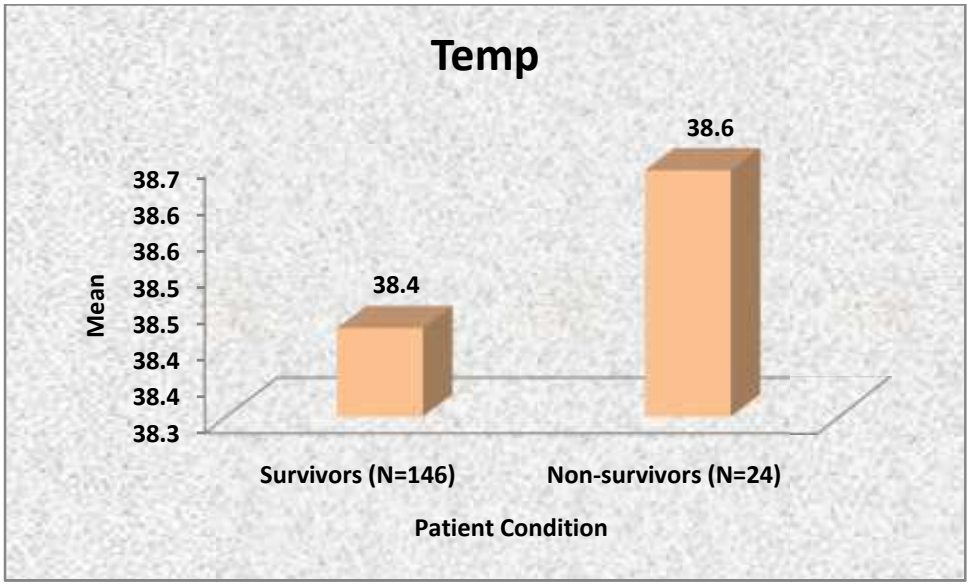


FIGURE-28 GRAPH SHOWING MEAN OF TEMPERATURE IN SURVIVORS AND NON SURVIVORS

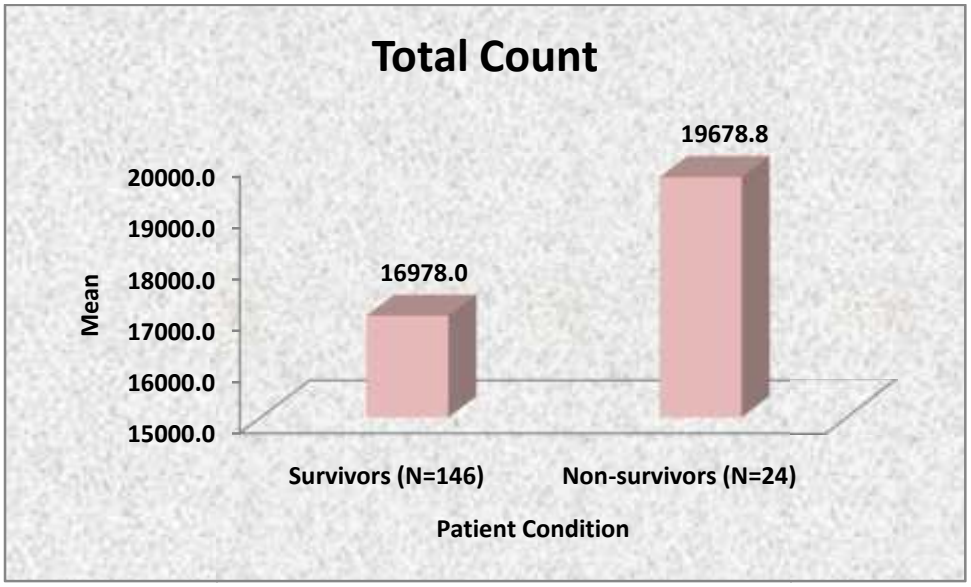


FIGURE-29 GRAPH SHOWING MEAN OF TOTAL COUNT IN SURVIVORS AND NON SURVIVORS

In present study it was observed that mean of total count was 16978 in survivors and 19678 in non survivors.

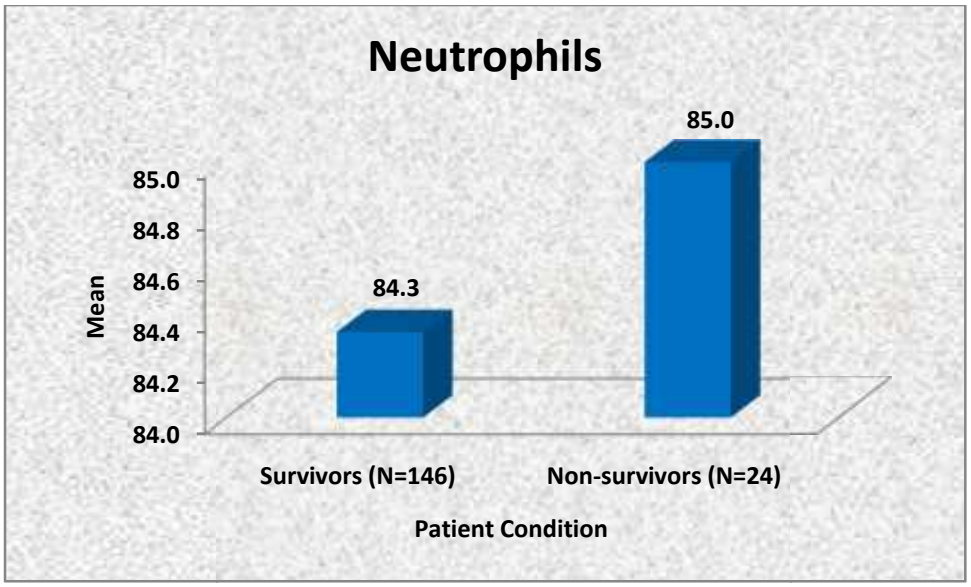


FIGURE-30 GRAPH SHOWING MEAN OF NEUTROPHILS(%) IN SURVIVORS AND NON SURVIVORS

In present study it was observed that mean of neutrophils was 84.3 in survivors and 85.0 in non survivors.

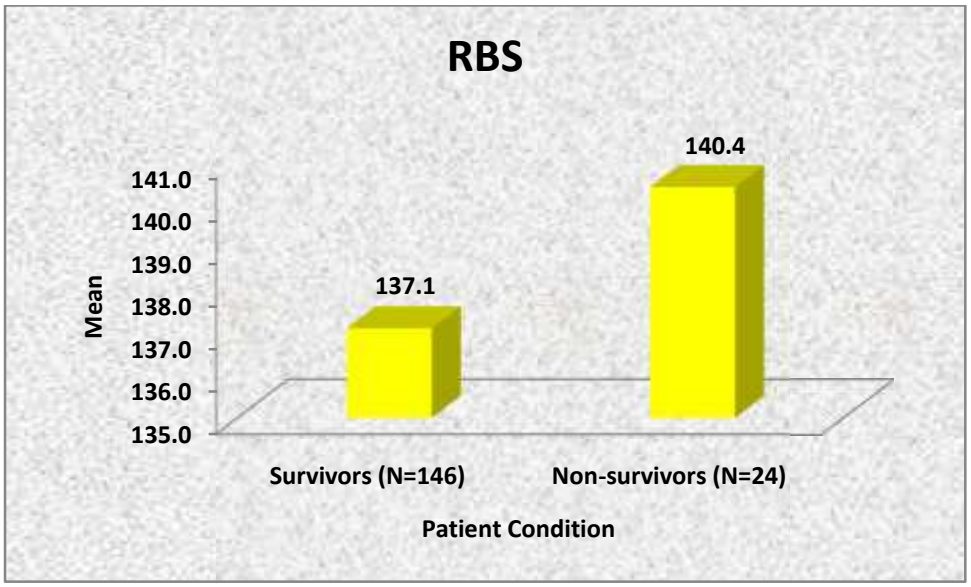


FIGURE-31 GRAPH SHOWING MEAN OF RANDOM BLOOD SUGAR IN SURVIVORS AND NON SURVIVORS

In present study it was observed that mean random blood sugar value was 137.1 in survivors and 140.4 in non survivors.

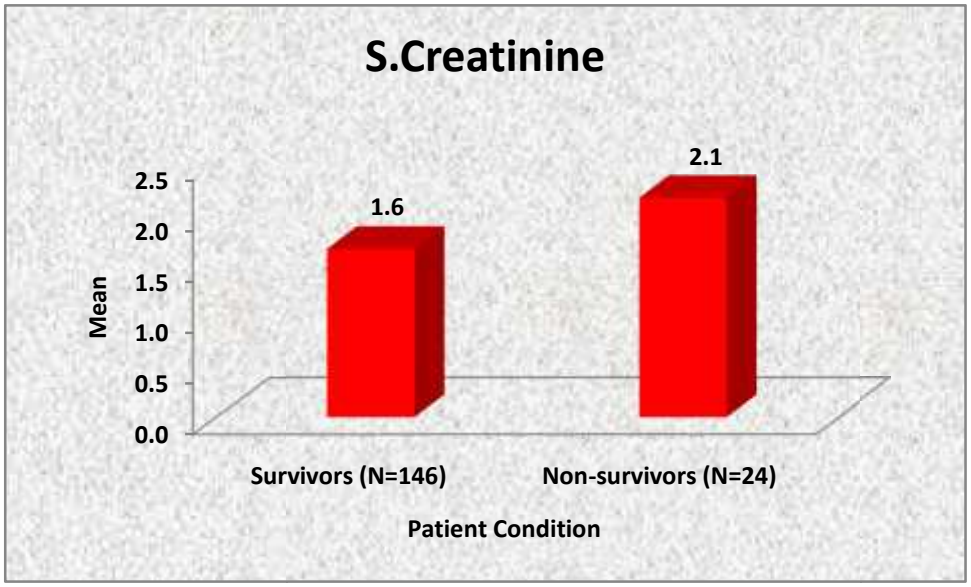


FIGURE-32 GRAPH SHOWING MEAN OF SERUM CREATININE IN SURVIVORS AND NON SURVIVORS

In present study it was observed that mean serum creatinine value was 1.6 in survivors and 2.1 in non survivors.

COMPARISON OF PARAMETERS WITH OTHER STUDIES:

TABLE-19 AGE AT PRESENTATION

STUDIES	SURVIVORS (YRS)	NONSURVIVORS (YRS)	P VALUE
MICHAEL D H et al[66]	63	74	<0.001
H.BRYANT et al[83]	64.7	65.1	0.89
C.VORWERK[84]	66.6	79.7	<0.0001
PRESENT STUDY	64.5	68.7	<0.292

In comparison with other studies present study shows mean of 64.5 yrs age in survivors group and 68.7yrs in non survivors group with p value of <0.292.

TABLE-20 : PULSE RATE

STUDIES	SURVIVORS (bpm)	NONSURVIVORS (bpm)	P VALUE
MICHAEL.D.H et al[66]	98	113	<0.001
H. BRYANT et al	87	117	0.85
PRESENT STUDY	99.6	105.2	<0.001 (significant)

In comparison with other studies present study shows mean value of pulse rate 99.6 in survivors and 105.2 in non survivors with p value of <0.001 which is significant.

TABLE-21 : RESPIRATORY RATE

STUDIES	SURVIVORS(cpm)	NONSURVIVORS(cpm)	P VALUE
MICHAEL.D.Het al	20	28	<0.001
H. BRYANT et al	19	30	-
PRESENT STUDY	23.8	24.5	<0.180

In comparison with other studies present study shows mean value of respiratory rate 23.8 cpm in survivors and 24.5cpm in non survivors with p value of <0.001 which is significant.

TABLE-22 : TEMPERATURE

STUDIES	SURVIVORS(^{0}C)	NONSURVIVORS(^{0}C)	P VALUE
MICHAEL.D.Het al	38.5	37.7	0.01
H. BRYANT et al	36.8	37.8	0.78
PRESENT STUDY	38.4	38.6	0.234

In comparison with other studies present study showed a mean temperature value of 38.4^0 C in survivors and 38.6^{0}C in non survivors with p value 0.234.

TABLE-23 : TOTAL COUNT

STUDIES	SURVIVORS	NONSURVIVORS	P VALUE
MICHAEL.D.Het al	11,000	13,300	0.01
H. BRYANT et al	15,500	13,300	0.33
PRESENT STUDY	16978	19,678	0.101

In comparison with other studies present study showed a mean total count of 16978 cells in survivors and 19678 cells in non survivors with p value 0.101.

SERUM CREATININE

TABLE-24

STUDIES	SURVIVORS(mg/dl)	NONSURVIVORS(mg/dl)	P VALUE
MICHAEL.D.Het al	1.0	1.3	<0.001
H. BRYANT et al	2.3	2.9	0.13
PRESENT STUDY	1.6	2.1	0.019(significant)

In comparison with other studies present study showed a mean value of serum creatinine 1.6 in survivors and 2.1 in non survivors with p value 0.019 which is significant.

TABLE-25 : SERUM LACTATE

STUDIES		**SURVIVORS(mmol/L)**	**NONSURVIVORS(mmol/L)**	**P VALUE**
MICHAEL. D.H et al		1.8	2.9	<0.001
H.BRYANT		6.1	8.0	0.01
C.VORWERK		3.6	5.0	0.0054
PRESENT STUDY	1ST SAMPLE	3.8	6.2	<0.001(significant)
	2ND SAMPLE	2.7	6.3	<0.001(significant)

The mean value of serum lactate 1st sample collected in survivors at the time of admission was 3.8 and the mean value of serum lactate second sample collected at 24-48 hrs after admission was 6.2.Highly significant difference is there between 1st and 2nd sample with p value <0.001 which is significant.

The mean value of serum lactate 1st sample collected in survivors at the time of admission was 2.7 and the mean value of serum lactate second sample collected at 24-48 hrs after admission was 6.3.Highly significant difference is there between 1st and 2nd sample with p value <0.001 which is significant.

TABLE-26 : SOURCE OF INFECTION

SOURCE OF INFECTION	EMANUEL RIVERS et al[85]	H.BRYANT et al[83]	STEPHEN TRZECIAK[86]	PRESENT STUDY
ABDOMINAL PATHOLOGY	10.11(%)	20.5%	19%	27.1%
ABSCESS	1.7%	5.1%	7%	20.0%
CELLULITIS,NECROTISING FASCITIS	23.11%	1.32%	9%	39.4%
URINARY COMPLICATION	27.2%	19.3%	24%	1.8%

In present study 27.1% of the patients presented with abdominal pathology and 39.4% of the patients presented with cellulitis, necrotisingfascitis and 20 % of the patients presented with abscess.

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DISCUSSION

Lactate is a product of anaerobic glucose metabolism. It is generated from pyruvatewith lactate dehydrogenase as a catalyst.Lactate is cleared from blood, primarily by the liver with the kidneys and skeletal muscles to a lesser degree.Serum Lactatewas chosen because the clearance of circulating lactateis prolonged inpatients with sepsis.

This study was conducted to evaluate the role of serum lactate as a prognostic marker in patients with sepsis. The serum lactate value was measured at the time of admission and the second sample within 24 to 48 hrs.

In present study the mean serum lactate value of first sample in survivors (146 patients) was 3.8 ± 1.2 and nonsurvivors(24 patients) was 6.2 ±1.9 with p value <0.001 which is significant. The serum lactate value of the second sample in survivors was 2.7 ±1.0 and in nonsurvivors was 6.3±1.8 with p value <0.001 which is significant.

Number of patients who recovered with decrease in the serum lactate value(compared to 1st and 2nd sample)-**120**(70.6%).

Number of patients who recovered with increase in serum lactate values(compared to 1st and 2nd sample)- **26**(15.3%).

Number of patients who died because of septic shock and associated comorbidities with significant increase in serum lactate values(serum lactate values > 4 in both 1st and 2nd sample- **16**(9.41%).

Number of patients who died within 2 days of admission with significant 1st sample serum lactate value(serum lactate value >4) – **8** (4.7%).

The present study can be compared to Michael D H et al and Bryant H et al with similar results. The mean value of serum lactate 1st sample collected at the time of admission was 4.1±1.6 and the mean value of serum lactate second sample collected at 24-48 hrs after admission was 3.1±1.6.Highly significant difference is there between 1st and 2nd sample with p value <0.001 which is significant.

Hence serum lactate is considered as a prognostic marker in patients with sepsis and evaluates the treatment outcome. Using lactate as an indicator of impaired metabolismin trauma and sepsis patients may help emergencycaregivers further diagnosis, risk stratify and treatpatients . Serial lactate measurements overthe early diagnostic and treatment period can assist inmonitoring treatment progress.

SUMMARY

In this study 170 patients admitted with sepsis in ShriB.M.Patil Medical College Hospital and Research centre, Vijayapurwere studied.

Maximum number of cases 53(31.2%) were observed in the age group 56-70yrs. There was male sex predomination,107(62.9%) male and 63(37.1%) females. 27.1% of the patients presented with abdominal pathology and 39.4% of the patients presented with skin ,cellulitis and necrotising fasciitis and 20 % of the patients presented with abscess.

The present study also demonstrated that lactate clearance resulted in a more significant mortality improvement. When implemented in a multidisciplinary hospital-wide fashion, routine measurement of lactate in patients with infection and possible sepsis can impact clinical assessment of mortality risk. Specifically , an initial lactate level of 4mmol/L or higher can have a substantial impact on pretest probability of acute phase death.

Present study reveals that initial serum lactate is a prognostic marker in patients with sepsis admitted. From this perspective, serial measurement of serum lactate on presentation seems to be a useful, simple strategy to identify at-risk severe sepsis patients.

CONCLUSION

The fall in lactate concentration following the initiation of treatment for sepsis is due to an attenuation of the stress response. Lactate levels are one of the most used biomarkers in sepsis. When their level is more than 4 mmol/L patients are at highest risk of mortality and an aggressive resuscitation strategy shall be warranted in these patients. The findings in our study suggest an important role for serial sampling of the subsequent two lactate values and lactate clearance as a prognostic indicator of sepsis. The patients with initial serum lactate value >4.0 mmol/L were independently associated with high mortality. It was clear that serum lactate had a positive correlation with outcome of sepsis.Hence serum lactate is considered as a independent and significant prognostic marker in patients with sepsis and evaluates the treatment outcome.

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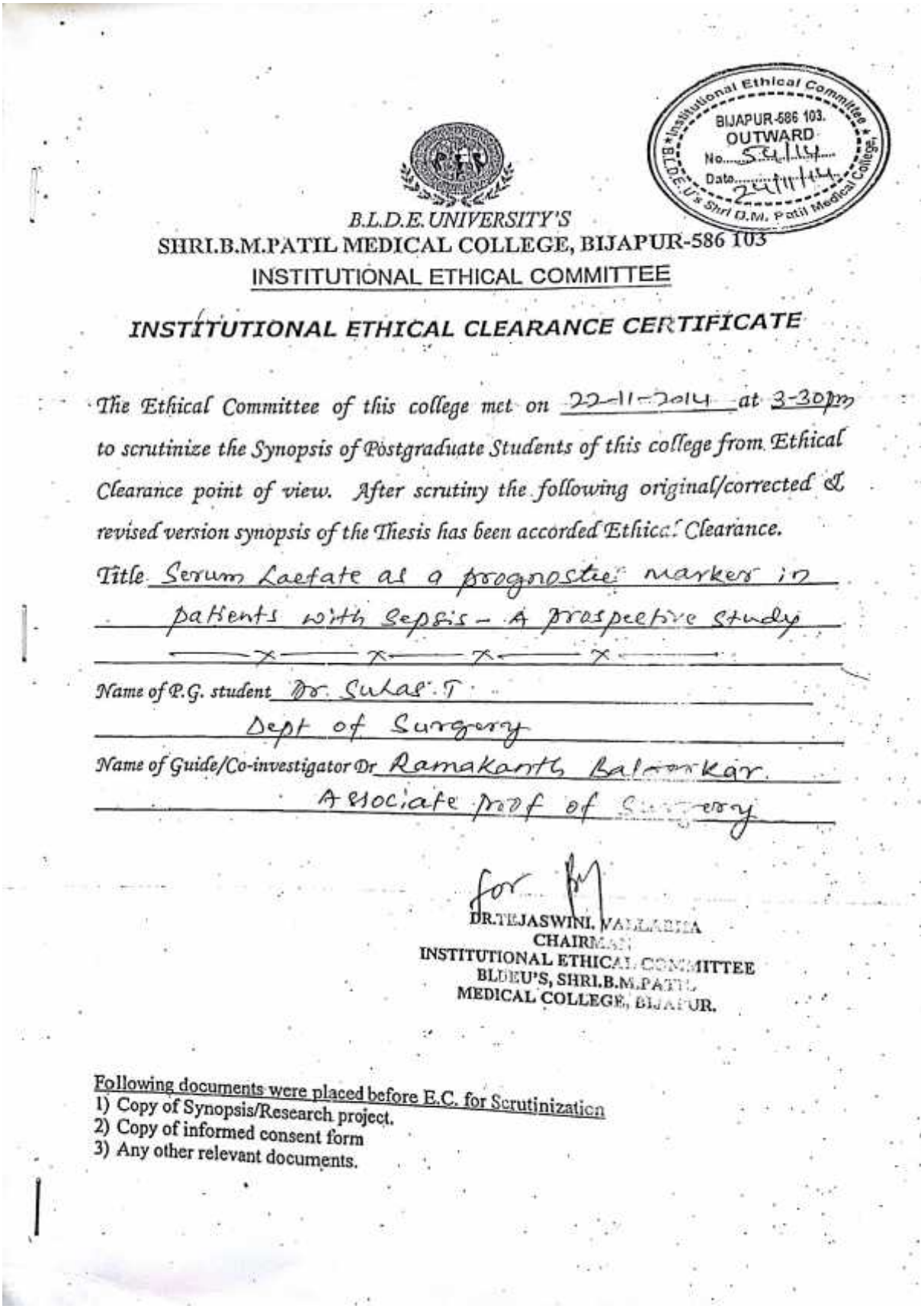
ANNEXURE-I



B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 22-11-2014 at 3-30pm to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.

Title Serum Lactate as a prognostic marker in patients with Sepsis - A prospective study

Name of P.G. student Dr. Sulas. T

Dept of Surgery

Name of Guide/Co-investigator Dr Ramakanth Balaorkar.

Associate Prof of Surgery

for

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

ANNEXURE – II

SAMPLE INFORMED CONSENT FORM

B.L.D.E.U.'s SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR – 586103, KARNATAKA

TITLE OF THE PROJECT : **Serum lactate as a prognostic marker in patients with sepsis.**

PRINCIPAL INVESTIGATOR: **Dr. Suhas.T.**
Department of General Surgery
Email: suhasshetty16@yahoo.co.in

PG GUIDE: **Dr. RamakanthBaloorkar**
Associate Professor of Surgery
B.L.D.E. University's
Shri B.M. Patil Medical College & Hospital& Research Centre,
Sholapur Road,
VIJAYAPUR – 586103.

PURPOSE OF RESEARCH:

I have been informed that this study will analyse the serum lactate as a prognostic marker in patients with sepsis.

I have been explained about the reason for doing this study and selecting me/my ward as a subject for this study. I have also been given free choice for either being included or not in the study.

PROCEDURE:

Patient will be explained about the need of the estimation of serum lactate as a prognostic marker in patients with sepsis.

BENEFITS:

Prevention of complications and to improve quality of life.

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of this hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. Information of a sensitive, personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code key connecting name to numbers will be kept in a separate secure location.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. Dr. Suhas T is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me.And that a copy of this consent form will be given to me to keep it and for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that Dr. Suhas T will terminate my participation in this study at any time after he has explained the reasons for doing so and has helped arrange for my continued care by my own physician or therapist, if this is appropriate.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly to my participation in this study, if such injury were reported promptly, then medical treatment would be available to me, but no further compensation will be provided.

I understand that by my agreement to participate in this study, I am not waiving any of my legal rights.

I have explained to _____ the purpose of this research, the procedures required and the possible risks and benefits, to the best of my ability in patient's own language

Date: Dr. RAMAKANTH BALOORKAR (Guide) Dr. SUHAS T (Investigator)

STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. SUHAS T has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project.

_____

_____

(Participant)
Date

_____

_____

(Witness to above signature)
Date

ANNEXURE III

PROFORMA

SL NO

NAME

AGE	IP NO
SEX	UNIT
RELIGION	DOA
OCCUPATION	DOO
ADDRESS	DOD

SOCIO-ECONOMIC STATUS

Complaints:

HISTORY OF PRESENT ILLNESS

A.HISTORY OF PAIN:

1. MODE OF ONSET

2. SITE OF PAIN

3. HOW LONG IS THE HISTORY OF PRESENTING COMPLAINT OF PAIN

4. DOES PAIN RADIATES

5. CHARACTER OF PAIN

6. RELIEF OF PAIN

7. NUMBER OF HOURS SINCE ACUTE PAIN STARTED.

B . FEVER

C. OTHERS

PAST HISTORY:

PERSONAL HISTORY: SMOKER/ALCOHOLIC

GENERAL PHYSICAL EXAMINATION

BUILT : WELL/MODERATE/POOR

NOURISHMENT : WELL/MODERATE/POOR

PALLOR

ICTERUS

FEBRILE

PEDAL EDEMA

GENERAL LYMPHADENOPATHY

NUTRITIONAL STATUS:

a. GENERAL APPEARANCE : NORAMAL/THIN

b. ANTHROPOMETRY : HT

WT

BMI

VITAL DATA:

TEMPERATURE :

PULSE :

RESPIRATORY RATE :

BLOOD PRESSURE :

LOCAL EXAMINATION:

INSPECTION:

PALPATION:

LOCAL RISE OF TEMPERATURE

TENDERNESS:

DISCHARGE IF ANY

SYSTEMIC EXAMINATION ACCORDING TO THE PRESENTATION OF SYMPTOMS :

PER ABDOMEN :

INSPECTION :

PALPATION :

PERCUSSION :

AUSCULTATION :

PER RECTAL :

RESPIRATORY SYSTEM

CARDIOVASCULAR SYSTEM

CENTRAL NERVOUS SYSTEM

CLINICAL DIAGNOSIS:

LABORATORY TESTS

SERUM LACTATE

HB%

TOTAL COUNT

DIFFERENTIAL COUNT

N/L/E/B/M:

URINE ROUTINE:

RBS

FBS

PPBS

B.UREA

S.CREATININE &

FOLLOWING INVESTIGATIONS AS PER THE PRESNTATION OF SYMPTOMS(AS AND WHEN REQUIRED.)

TOTAL PROTEIN

S.ALBUMIN

SERUM ELECTROLYTES

Na

K

Cl

Ca

BLOOD GROUPING

HIV

HBsAg

CHEST X RAY:

ERECT ABDOMEN X-RAY:

ULTRASONOGRAPHY OF ABDOMEN AND PELVIS:

OTHERS: