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# 1. INTRODUCTION

## 1.1 Evolution and significance of Sepsis:

The word "sepsis" has its origin from a Greek word for decomposition or putrefaction, and has been used in that context since before Hippocrates (Geroulanos and Douka, 2006). However, although the word, sepsis, has been used for more than 2700 years, it is only relatively recently that we have begun to understand the pathophysiology of sepsis in any depth (Vincent and Abraham, 2006).

Till 1991, there was no concrete definition of sepsis so the American College of Chest Physicians and the Society of Critical Care Medicine held a consensus conference in 1991 with the goal of standardizing definitions for sepsis and related disorders. They defined "infection" as a microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms. "Bacteremia" was defined as the presence of viable bacteria in the blood. "Systemic inflammatory response syndrome" (SIRS) was defined as the systemic inflammatory response to a variety of severe clinical insults (Bone et al., 1992). The response is manifested by 2 or more of the following conditions (figure - 1):

1. Body temperature greater than 38 °C or less than 36°C
2. Heart rate greater than 90 beats/min
3. Respiratory rate greater than 20 breaths/min or hyperventilation with a PaCO₂ less than 32 mmHg
4. White blood cell count >12000/mm³, <4000/mm³, or with >10% immature neutrophils.

However, with continuing advances in our understanding of sepsis pathophysiology, identification of various proposed sepsis markers, and persistent uncertainty and disagreement about the usefulness of the SIRS criteria, a Sepsis Definitions conference was convened in 2001 to re-evaluate and update definitions. A new model has been proposed (PIRO) which allows an earlier and more objective (measurable) assessment of the clinical condition of the patient. This model integrates a number of currently available parameters, which describe the Predisposition, the Infection, the Response and the Organ dysfunction (Levy et al., 2003).

Sepsis is the most common cause of death in the intensive care unit (ICU) and the thirteenth leading cause of death in the United States. A multicentric prospective
study in India showed that 25% patients in the ICU had SIRS with organ dysfunction of which 52.77% was due to sepsis and 16.45% was due to severe sepsis. The 28-day mortality of severe sepsis was 64.6% (Todi et al., 2010). Worldwide the mortality associated with these conditions ranges from around 26% in patients with SIRS to around 82% in septic shock (Salvo et al., 1995). The incidence continues to increase, with unacceptably high mortality rates, despite the use of specific antibiotics, aggressive operative intervention, nutritional support, and anti-inflammatory therapies. In addition to high mortality, patients with severe sepsis or early septic shock spend prolonged periods of time in the ICU and are significantly more expensive to treat than ICU patients without sepsis. It therefore continues to have significant clinical and financial implications and remains an area that attracts intense research interest.

\[ \text{Figure 1: Sepsis represents SIRS with infection} \]

1.2 Spectrum of Sepsis:

"Sepsis" was defined as the systemic response to infection, manifested by 2 or more of the conditions listed above for SIRS. "Severe sepsis" was defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status. "Septic shock" was defined as sepsis-induced
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hypotension despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured. "Sepsis-induced hypotension" was defined as a systolic blood pressure lower than 90 mm Hg or a reduction of 40 mm Hg or more from baseline in the absence of other causes for hypotension. "Multiple organ dysfunction syndrome" was defined as the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

It is important to note that SIRS is a clinical syndrome resulting from systemic inflammation, potentially from a wide variety of causes. Sepsis is the term used when systemic inflammation is due to an infection.

It can develop rapidly. The sooner it is diagnosed and treated, the better. The most frequent sites of infection leading to sepsis are the lung, urinary tract, abdomen, and pelvis. In up to 30 percent of patients, however, a definite source of infection cannot be identified. The course of the disease may be unpredictable. Some patients may deteriorate fast while others suffer from varying degrees of organ dysfunction or failure, but most will recover with treatment. Sepsis therefore, is part of a spectrum of conditions ranging from the systemic inflammatory response syndrome (SIRS) to septic shock and multiple organ dysfunction syndromes (MODS).

1.3 Pathophysiology of sepsis:
The pathophysiology of sepsis has been divided into five stages:
1) The infectious insult
2) The preliminary systemic response
3) The overwhelming systemic response
4) Compensatory anti-inflammatory reaction
5) Immunomodulatory failure

Sepsis is characterised by a systemic inflammatory response (SIRS) to an infective insult (Figure 1). The inflammatory response results in systemic vasodilatation, hypotension, increased cardiac output and, eventually, reduced oxygen extraction by the tissues. The key pathological features driving this process are abnormalities of
endothelial function and disordered coagulation homeostasis. These result in the release of a variety of cytokines and tissue factors, an activation of the clotting cascade and a reduction in the natural inhibitors of clotting (e.g. activated protein C). Once triggered, the downward spiral of severe sepsis is believed to be independent of the underlying infectious disease process. The combination of increased thrombosis and reduced fibrinolysis leads to disturbed microcirculatory blood flow, microcirculatory ischaemia, and multiple organ dysfunction and eventual multiple organ failure.

1.4 Pathophysiology of Oxidative stress in Sepsis:

Formation of Free radicals:
During chemical processes, molecules can be reduced or oxidized. Reduction and oxidation can leave the molecule unstable and free to react with other molecules to cause damage to cell membranes, proteins, and DNA. These reduced substances are called free radicals.

Reactive oxygen species (ROS) are molecules or atoms formed by reduction of oxygen; can be either free radicals or non-radicals. The most commonly known ROS are superoxide (\(O_2^-\)), hydrogen peroxide (\(H_2O_2\)), and the hydroxyl radical (\(OH^-\)). \(O_2^-\) is relatively innocuous, however, its reaction with other radicals like nitric oxide and iron clusters in some of the enzymes makes it the mother of potent reactive species. The mitochondrial respiratory chain is the most important site of \(O_2^-\) generation (Halliwell and Gutteridge, 2007). In biological tissues \(O_2^-\) can be dismutated to non-radical species \(H_2O_2\) by the activity of the enzyme superoxide dismutase (SOD). Hydrogen peroxide is produced continuously in all cells and is often employed as a signalling molecule. Although not a free radical, it has a great physiological relevance because of its ability to penetrate biological membranes and to act like an intermediate in the production of more reactive oxygen species, namely hydroxyl radical and hypochlorous acid (Nordberg and Arner, 2001). It does not readily oxidize most proteins, lipids or DNA but is cytotoxic at micromolar concentrations and has been implicated in number of diseased states (Pryor et al., 2006).

Hydrogen peroxide when acted upon by catalase (CAT) is converted to water and molecular oxygen or otherwise highly reactive hydroxyl radicals can be formed in presence of metal ions like \(Fe^{2+}\) (Figure 2). Hydroxyl free radicals are much more
reactive than superoxide anions. The ROS, $O_2^-$, $H_2O_2$, and $OH^-$ are responsible for damage to lipids, proteins, and DNA. Hydroxyl radicals can initiate lipid peroxidation in the cell membrane by eliminating hydrogen from the unsaturated fatty acids. This reaction can cause cell death and can induce an inflammatory response. As neutrophils invade, they release more ROS and the cycle continues. Proteins, particularly enzymes, are also damaged by ROS.

Normally majority of ROS are formed during cellular respiration and by activated phagocytic cells, including neutrophils, involved in the inflammatory response. They have physiologically essential roles in mitochondrial respiration, prostaglandin production pathways and host defence.

Under normal physiological conditions, a homeostatic balance exists between the formation of reactive oxidizing/oxygen species and their removal by endogenous antioxidant scavenging compounds. **Oxidative stress** occurs when this balance is disrupted by excessive production of ROS, including superoxide, hydrogen peroxide and hydroxyl radicals, and/or by inadequate antioxidant defences, including SOD, CAT, glutathione peroxidase (GPx), vitamins C and E, and glutathione (GSH). Both may occur in sepsis.

Researchers have demonstrated evidence of oxidative stress in sepsis (Espat et al., 2000; Metnitz et al., 1999) causing damages mediated by ROS (Figure – 3). Oxidation of DNA and proteins may take place, along with membrane damage because of lipid peroxidation, leading to alterations in membrane permeability, modification of protein structure and functional changes. Oxidative damage to the mitochondrial membrane can also occur, resulting in membrane depolarization and the uncoupling of oxidative phosphorylation, with altered cellular respiration. This can ultimately lead to mitochondrial damage, with release of cytochrome c, activation of caspases and apoptosis (programmed cell death). Further, the ROS can stimulate the inflammatory system by causing an increase in cytokines (eg, interleukins, tumor necrosis factor) and cell adhesion. Endothelial cells are stimulated to increase vascular permeability, causing capillary leakage. Neutrophils and macrophages are chemically attracted to areas of lipid peroxidation, causing these phagocytes to migrate into tissues and release more ROS (Figure – 4). Both cytokines and ROS can enter the circulation and mediate many systemic inflammatory responses linked with clinical conditions.
In septic shock the ischaemia of tissue beds followed by reperfusion with oxygenated blood, during resuscitation, leads to significant production of ROS. This is primed by the increased activity of xanthine oxidase and increased production of hypoxanthine due to loss of adenosine triphosphate during ischemia. When oxygen is reintroduced,

**Figure 2:** Generation of reactive oxygen species and the defense mechanisms against damage by active oxygen. During hypoxia superoxide generated may be degraded into the mitochondria by Mn-SOD or, if it reaches the cytosol, by Cu-SOD. In the endoplasmic reticulum, NADPH-cytochrome p450 reductase can leak electrons onto O$_2$ generating O$_2^{-}$. FADH$_2$ and cytochrome b$_5$ can also contribute to this system. Within peroxisomes, there are enzymes localized that produce H$_2$O$_2$ without intermediation of O$_2^{-}$. Contrarily to O$_2^{-}$, H$_2$O$_2$ is able to cross cell membranes and within cells it can react with Fe$^{2+}$ or Cu$^{+}$ to form hydroxyl radicals via Fenton reaction. GR= glutathione reductase; MPO= myeloperoxidase; RE=endoplasmic reticulum; $^{1}$O$_2$= singlet oxygen. (Adapted from: Mates JM, Perez-Gomez C, De Castro IN. Antioxidant enzymes and human diseases. Clin Biochem 1999;32:595-603.)
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Membrane phospholipids

Isoprostanes

Arachidonic acid release

COX-1/2

LO

PGs

TXA2

LTs

Modulation of second messengers

PAF

VASCULAR FUNCTION & STRUCTURE

Oxidative stress

Activated leukocytes

Substrate oxidations

High PO2

ROS

Antioxidant regulation

H2O2

O2·-

NO·

HOCI

Fe2+ /Fe3+

高级OX

ONOO-

Antioxidant protection

Lipids

Oxidation, hydroxylation, chlorination, nitration

Proteins

Peroxides, aldehydes RO2, RO2 (HNE)

DNA

Base damage

Sew damage

Antioxidant repair

GCMS detection

Figure 3: The possible role of reactive oxygen species (ROS) in modulating the effects of inflammation on vascular structure and function. (Adopted from: Gutteridge JMC and Mitchell J. IN Redox imbalance in the critically ill. Brit Med Bull 1999;55 (No. 1): 49-75)

1.5 Markers in Sepsis:

1.5.1 Established haematological markers and C-reactive protein (CRP): Sepsis is a challenge in medicine. The diagnosis can be difficult despite all the laid down criteria since the clinical signs (tachycardia, leucocytosis, tachypnoea, and pyrexia) often overlap with other non-infectious causes of systemic inflammation such as trauma, surgery and hypoxia (Levy et al., 2003). Microbiological cultures are often used to distinguish sepsis from non-infectious conditions. However, this method lacks sensitivity and specificity, and there is often a substantial time delay between collecting the sample and obtaining a definitive result. Delays in diagnosis and treatment of sepsis can result in rapid progression to circulatory collapse, multiple organ failure, and eventually death. Whereas accurate and timely diagnosis of sepsis
has the potential to limit morbidity, reduce costs, and improve patients' outcome (Gao et al., 2005).

Figure 4: The scavengers' superoxide dismutase, catalase, and glutathione are responsible for inactivation of reactive oxygen species (ROS) and thus provide a defense against lipid peroxidation, protein damage, and DNA damage due to ROS. (Adopted from: Goodyear-Bruch C, Pierce JD. Oxidative Stress in Critically Ill Patients. Am J Crit Care 2002;11:543-51.)

Various markers have been proposed over the years. Cytokine levels may seem an obvious choice as cytokines are key mediators of the inflammatory response to sepsis. Raised levels of certain cytokines have been well documented in patients with sepsis and some have been correlated with outcome (Calandra et al., 1990; Pinsky et al., 1993; Terregino et al., 2000; Gogos et al., 2000). However, no cytokine is specific for sepsis, and not all cytokine levels are raised at all time points during the course of the disease. Other markers of inflammation have also been suggested as being of use in the diagnosis of sepsis and some, such as C-reactive protein (CRP), are in common use, particularly in Europe. CRP has been shown to be a useful indicator of the
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presence of sepsis (Matson et al., 1997), and more indicative of infection than the white cell count or fever (P’ovoa et al., 1998). CRP levels >17 mg/dl have been suggested as providing a means of separating patients with sepsis from those with a non-septic inflammatory response due to trauma (Miller et al., 1999).

Many other molecules have been suggested as markers of sepsis, but all are markers of inflammation rather than infection, and none are specific for sepsis. The development of multiplex technology now allows the presence of multiple markers to be detected from a single blood sample, enabling a so-called “sepsis profile” to be constructed for individual patients. Though blood cultures play a central role in the diagnosis of blood stream infection in today’s clinical practice, the traditional blood culture tests are slow (usually taking several days), and are not very sensitive (particularly if the patient has already received antibiotics).

1.5.2 Proposed biochemical markers of sepsis:

A number of circulating inflammatory markers have been investigated as tools to facilitate the early recognition of sepsis. These include pro-calcitonin; IL-6; direct measurement of endotoxin, TREM-1, lipoprotein binding protein and triggering receptor on myeloid cells (Opal, 2007; Meisner, 2005). Pro-calcitonin has shown the most promise as a biomarker of early sepsis. It fulfills several criteria of clinical needs: it responds both to infection and severity of inflammation and thus has an impact on therapy. Recent studies indicate that antibiotic treatment can also be guided by procalcitonin (Christ-Crain and Muller, 2007). However a recent systematic review of trials of critically ill patients with sepsis concluded that procalcitonin cannot reliably differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome in critically ill adult patients arguing against the routine use of procalcitonin test in critical care settings (Tang et al., 2007).

Critical illness can drastically increase the production of ROS and other radicals. This compromises antioxidant capacity and leads to enhanced oxidative stress (Crimi et al., 2005). Sources of oxidative stress in critical illness include activation of phagocytic cells; excessive peroxynitrite production by vascular endothelium; release of iron, copper, and metalloprotein; and damage caused by tissue and vascular ischemia/reperfusion. Thus, many biological indicators of oxidative damage are being investigated in clinical trials, and the results may assist clinicians in determining if ROS damage is occurring. In addition to laboratory values that indicate production of
ROS, measurements of antioxidant levels (α-tocopherol, β-carotene, selenium) and enzyme activity (SOD, CAT, GPX) have been investigated in patients thought to have oxidative stress. Further clinical research is needed to determine which biomarker or indicator is the most specific and sensitive sign of oxidative stress.

Various studies have documented reduced plasma enzymatic and non-enzymatic antioxidants are an indirect evidence of increased oxidative stress (Table 1). Reduced levels of plasma α-tocopherol accompanied by increased plasma thiobarbituric acid-reactive substance (TBARS) levels in critically ill patients compared with controls, suggests increased lipid peroxidation (Takeda et al., 1984; Goode et al., 1995). Similarly, Borrelli et al., (1996), and Galley et al., (1997), documented significantly decreased plasma vitamin C and elevated lipid peroxides in ICU patients who developed multiple organ failure compared with those who did not. Further, there is decreased total antioxidant potential in patients with sepsis and secondary organ dysfunction, associated with non-survival (Cowley et al., 1996). Increased xanthine oxidase, SOD and GPX activity has been reported in patients with sepsis or SIRS in both adult (Galley et al., 1996 a) and paediatric populations (Batra et al., 2000) suggesting increased production of reactive oxygen species in paediatric population also. The roles of ROS and xanthine oxidase activity in relation to the severity of sepsis and organ dysfunction have been studied. Galley et al., (1996 a), found that critically ill patients with sepsis who died had lower levels of xanthine oxidase, greater production of free radicals, and higher levels of lactate than did critically ill patients with sepsis who lived. This finding suggests that ROS generation plays a key role in survival for sepsis patients.

GSH metabolism is altered in sepsis. Rapid depletion of intracellular GSH in human and animal endothelial and epithelial cells occurs in response to tumor necrosis factor α (TNF-α) in vitro because of oxidation of GSH to GSSG, followed by rebound increases in GSH synthesis as a result of up-regulation of the enzyme γ-glutamylcysteine synthetase (γGCS) (Malmezat et al., 2000; Carbonell et al., 2000).
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<td>Thiobarbituric acid–reacting substances</td>
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Present, therefore rely on the presence of a combination of clinical markers and the biochemical markers. Among the various oxidative stress markers the most significant is yet to be evaluated. Further, there is not much literature on the co-relation between the level of these markers and the severity of sepsis (Macdonald et al., 2003). Further clinical research is needed to determine which biomarker or indicator is the most specific and sensitive sign of oxidative stress.
1.6 Strategies to enhance endogenous antioxidants:
To combat the threat of oxidative stress, there exist a number of endogenous antioxidant defences. These include vitamins E and C, pro-vitamin A (β-carotene), glutathione peroxidase, glutathione-S-transferase, superoxide dismutase and catalase, bilirubin, urate, and other plasma proteins. These antioxidants can be divided into enzymatic and nonenzymatic groups.

The enzymatic antioxidants include superoxide dismutase (the primary antioxidant enzyme that acts on ROS), which catalyzes the conversion of O$_2^-$ to H$_2$O$_2$ and molecular oxygen; catalase, which then converts H$_2$O$_2$ to H$_2$O and O$_2$, and glutathione peroxidase, which reduces H$_2$O$_2$ or other hydroperoxides to H$_2$O by oxidizing glutathione (GSH). Glutathione-S-transferase similar to GPX, also rids cells of hydroperoxides but does not act upon H$_2$O$_2$. Re-reduction of the oxidized form of glutathione (glutathione disulfide) is then catalyzed by glutathione reductase.

The nonenzymatic antioxidants include the lipid soluble vitamins (vitamin E, and vitamin A or β-carotene) and the water-soluble vitamins (vitamin C) glutathione. Vitamin E has been described as the major chain-breaking antioxidant in humans. Vitamin C (ascorbic acid), obtained primarily from citrus fruits, functions as a water-soluble antioxidant capable of broadly scavenging ROS, including the major neutrophil oxidants: H$_2$O$_2$, and hypochlorous acid.

Vitamin C (ascorbic acid) is a powerful electron donor, reacting with both superoxide and hydroxyl radicals. Ex vivo studies demonstrated regulation of cellular activity by exogenous ascorbic acid, in that the increased adherence of, and superoxide anion production by, macrophages from mice with endotoxic shock were lower in the presence of ascorbic acid (Victor et al., 2000). In a rat caecal ligation and puncture model, exogenous administration of ascorbic acid protected against compromised microvascular perfusion. In vitro studies showed that ascorbic acid inhibited the replication of bacteria and prevented hydrogen peroxide injury to cultured microvascular endothelial cells. In guinea-pigs, which, like humans, cannot synthesize their own vitamin C, administration of endotoxin rapidly depleted vitamin C stores; repletion prevented oxidative damage (Rojas et al., 1996) However, in another study using infusion of live bacteria, mortality was only improved in guinea-pigs receiving high doses of vitamin E; high doses of vitamin C did not improve survival (Peck and Alexander, 1991). Circulating concentrations of vitamin C are markedly depleted in
patients with sepsis. Markedly different handling of infused ascorbate compared with healthy subjects was reported, and administration of vitamin C in conjunction with other antioxidants failed to ameliorate free radical-mediated damage (Galley et al., 1997).

N-acetylcysteine is a sulphydryl donor which can replete intracellular GSH by donating cysteine; however, the GSH synthesis enzymes are necessary. GSH monoester does not require γGCS or glutathione synthetase. In animal studies, increased survival on exposure to endotoxin, decreased cytokine and adhesion molecule expression, decreased oxidative stress and inhibition of NFκB have been demonstrated in response to administration of N-acetylcysteine. Pretreatment with N-acetylcysteine before endotoxin administration resulted in decreased NFκB activation, (Blackwell et al., 1996) lower TNF-α release and increased survival (Zhang et al., 1994). However, in a murine caecal ligation and puncture model of sepsis, improved survival after N-acetylcysteine treatment was not associated with lower TNF-α or increased liver GSH content (Villa et al., 1995). Administration of N-acetylcysteine along with α-tocopherol (vitamin E) suppressed NFκB activation and with vitamin E and β-carotene it reduced lipid peroxidation and restored GSH levels in endotoxic rats (Kheir-Eldin et al., 2001).

In the clinical setting, N-acetylcysteine alone and in combination with other antioxidants has been shown to have variable results. In a randomized, placebo-controlled trial, Paterson and colleagues, (2003), found a reduction in mononuclear leucocyte NFκB activation after infusion of N-acetylcysteine in patients with sepsis. When N-acetylcysteine was administered in conjunction with ascorbic acid and α-tocopherol in patients with septic shock, neither total antioxidant capacity nor lipid peroxidation was changed (Galley et al., 1997). Various studies also showed that administration of high doses of N-acetylcysteine plus GSH significantly decreased markers of oxidative stress in patients with septic shock (Ortolani et al., 2000; Peake et al., 1996). Although Spapen and colleagues (2008), did show a significant improvement in oxygenation and static lung compliance at 24 h and reduced IL-8 levels in N-acetylcysteine-treated patients, in none of these trials was survival improved. However, these small studies were not powered to detect changes in mortality.
The enzymatic and nonenzymatic antioxidant systems are intimately linked to one another. Both vitamin C and GSH have been implicated in the recycling of α-tocopherol radicals. The complex interactions of these different antioxidant systems may imply that successful therapeutic strategies will depend on the use of a combination of various antioxidants rather than a single agent.

1.7 Hypothesis
The complex antioxidants enzymes in the body would always try to counteract the reactive species so as to reduce the cellular damage. This could lead to either an upsurge of the antioxidants or a decrease in the levels of antioxidants so much so that the ROS would take the upper hand and cause cellular damage.

We therefore aim to evaluate the extent of oxidative stress. We hypothesize that the measurements of the levels of antioxidant enzymes in the serum following septic peritonitis could be an indirect evidence of the 1) the oxidative stress 2) the severity of sepsis 3) the rise in the level of enzymes if any following antibiotic therapy would indicate its role in combating this stress, 4) the rise in the levels of enzymes if any following administration of exogenous antioxidants (vitamin C and or N-acetylcysteine) would indicate their role in reducing the stress (Rojas et al., 1996; Kheir-Eldin et al., 2001).

1.8 Scope
The prospect of finding the ideal therapeutic antioxidant agent increases as the quest to elucidate the precise cellular and molecular interactions in sepsis continues to yield intriguing information (Macdonald et al., 2003).

Sepsis therefore remains a major challenge in medicine. It is a common and frequently fatal infectious condition. The incidence continues to increase, with unacceptably high mortality rates, despite the use of specific antibiotics, aggressive operative intervention, nutritional support, and anti-inflammatory therapies. Typically, septic patients exhibit a high degree of heterogeneity due to variables such as age, weight, gender, the presence of secondary disease, the state of the immune system, and the severity of the infection. We are at urgent need for biomarkers and reliable measurements that can be applied to risk stratification of septic patients and that would easily identify those patients at the highest risk of a poor outcome. Such markers would be of fundamental importance to decision making for early intervention therapy or for the design of septic clinical trials.
In most of the previous studies the rise of a particular free radical in the plasma due to oxidative stress in sepsis was evaluated. Very few studies have undertaken a comparative study on the different free radical/antioxidant markers. The previous observations predominantly are based on animal studies. Human studies on the evaluation of free radicals are mostly in Acute Respiratory Distress Syndrome, pulmonary sepsis and neurosurgical patients.

A number of antioxidants (N-acetylcysteine, vitamin C, alpha tocopherol etc.) have been used to combat the product of oxidative stress. However, the previous studies have shown a mixed response, probably because of small sample size and short course of drug therapy. The effect of antioxidants on oxidative stress has been observed predominantly in animals. There is no randomized, placebo controlled human trial. Vitamin C (also known as poor man’s antioxidant) and N-acetylcysteine are reasonably cheap, easily available, with similar dose schedule and can be given both orally and intravenously. These qualities could be an added advantage especially in patients with poor socioeconomic status suffering septic peritonitis where the drugs cannot be administered orally.

Hence, it would be our endeavour to evaluate the most significant oxidative stress marker in sepsis, its co-relation with the severity of sepsis and the antioxidant (vitamin C or N-acetylcysteine) that is most effective in reducing the level of various oxidative stress markers. This study was conducted for the first time to the best of our knowledge.

1.9 Aims / Objectives

To evaluate:

1) the most significant oxidative stress marker(s) in sepsis

2) the correlation of the level of sepsis markers (haematological and biochemical) with that of the severity of sepsis

3) the antioxidant agents (N-acetylcysteine and vitamin C) most effective in reducing the level of sepsis markers (haematological and biochemical markers) in sepsis.