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REVIEW

Sepsis: Evidence-based pathogenesis and treatment

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Abstract

Sepsis can develop during the body's response to a critical illness leading to multiple organ failure, irreversible shock, and death. Sepsis has been vexing health care providers for centuries due to its insidious onset, generalized metabolic dysfunction, and lack of specific therapy. A common factor underlying sepsis is the characteristic hypermetabolic response as the body ramps up every physiological system in its fight against the underlying critical illness. A hypermetabolic response requires supraphysiological amounts of energy, which is mostly supplied *via* oxidative phosphorylation generated ATP. A by-product of oxidative phosphorylation is hydrogen peroxide (H_2O_2), a toxic, membrane-permeable oxidizing agent that is produced in far greater amounts during a hypermetabolic state. Continued production of mitochondrial H_2O_2 can overwhelm cellular reductive (antioxidant) capacity leading to a build-up within cells and eventual diffusion into the bloodstream. H_2O_2 is a metabolic poison that can inhibit enzyme systems leading to organ failure, microangiopathic dysfunction, and irreversible septic shock. The toxic effects of H_2O_2 mirror the clinical and laboratory abnormalities observed in sepsis, and toxic levels of blood H_2O_2 have been reported in patients with septic shock. This review provides evidence to support a causal role for H_2O_2 in the pathogenesis of sepsis, and an evidence-based therapeutic intervention to reduce H_2O_2 levels in the body and restore redox homeostasis, which is necessary for normal organ function and vascular responsiveness.

Key Words: Sepsis; Septic shock; Redox homeostasis; Thiosulfate; Hydrogen peroxide

Core Tip: Sepsis mortality remains unacceptably high because there is no specific treatment to prevent or reverse the multiple organ failure and refractory hypotension that develops in this condition. An evidence-based analysis suggests that impaired

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systemic redox homeostasis caused by the toxic accumulation of hydrogen peroxide has a causal role in the pathogenesis of this often fatal illness. The data imply that restoration of redox homeostasis by therapeutic reduction of hydrogen peroxide will significantly reduce the morbidity and mortality associated with sepsis. A therapeutic intervention to reduce systemic levels of hydrogen peroxide is presented.

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INTRODUCTION

Medicine has made fantastic strides over the past century. Our intricate knowledge of disease has been spearheaded by amazing advances in laboratory techniques that allow us to identify and instigate changes at the molecular level. This has led to an explosion of data accompanied by a detailed insight into pathological processes that perpetuate disease states leading to the identification of potential therapeutic targets, which can be exploited for new and more effective therapeutic interventions. However, while laboratory research is an extremely useful tool to obtain a pathophysiological snapshot of disease it cannot, on its own, identify the pathogenesis, and for some diseases, a creative theoretical approach is the only way to get "upstream" where novel insights may shed light on difficult clinical problems.

A prime example is sepsis, a systemic process with a high fatality rate that ultimately leads to microangiopathic dysfunction, refractory hypotension, multiple organ failure, and death. Worldwide, someone dies of sepsis every 3 s with 20% of global deaths being sepsis-related for a total of 11 million deaths annually and growing. Sepsis is thought to be a hyper-immune response to infection[1]. But in over 40% of sepsis cases there is no identifiable infectious agent, and culture positivity is not independently associated with mortality in sepsis[2-6]. These observations suggest that infection can be sufficient but is not absolutely necessary for sepsis to develop. It also suggests an endogenous process that is common to both infectious and non-infectious conditions (*i.e.*, multiple body trauma, pancreatitis, post-surgery, *etc.*), which is set in motion, ultimately leading to sepsis. Finally, the profound immunosuppression occurring during sepsis[7] suggests a non-immune contemporaneous process as the proximate causal factor in the development of the sepsis syndrome. This raises the consideration that the immune system is failing for the same reason other organs fail.

From a metabolic perspective, there is evidence of impaired mitochondrial oxygen utilization in sepsis despite normal oxygen tension[4,8-10]. This suggests a mitochondrial-derived agent capable of interfering with oxygen utilization by inhibiting substrate oxidation during the tricarboxylic acid (Krebs) cycle or oxidative phosphorylation. The close association of hyperlactatemia with adverse sepsis outcomes despite the absence of tissue hypoxia or impaired tissue oxygenation provides further evidence that implicates impairment of mitochondrial oxidative metabolism as discussed in more detail below[11,12].

The identification of mitochondrial abnormalities in sepsis focuses attention on bioenergetics and suggests that the common link between infectious and non-infectious origins of sepsis is not an immune response but a hypermetabolic state that sends mitochondrial metabolism into “overdrive” causing dysfunction of vital intramitochondrial bioenergetic processes. This reduces the problem of sepsis to the identification of a mitochondrial-generated molecule whose production is scaled up during hypermetabolism and is capable of inhibiting enzymes in the Krebs cycle and/or the electron transport chain (ETC). This is likely to be a small molecule that is normally eliminated within mitochondria since most people do not develop sepsis during a clinical hypermetabolic response.

A prime element that fulfills these theoretical requirements is hydrogen peroxide (H_2O_2), a small, cell-membrane permeable highly toxic oxidizing agent that is produced within mitochondria as a result of electron transport chain auto-oxidation [13]. H_2O_2 must be immediately eliminated to prevent cell damage and is removed by

the following series of reactions (Figure 1)[14-16].

Studies have shown that blood H_2O_2 is significantly elevated in human sepsis and septic shock with values reported up to 558 μmol/L, which is over 100 times the normal upper limit of 5 μmol/L and over ten times 50 μmol/L upper limit at which H_2O_2 becomes cytotoxic[17-19]. Certain cell populations, such as lymphocytes, undergo apoptosis at H_2O_2 exposure of less than 1 μmol/L, which can lead to significant lymphopenia and immunosuppression[19,20]. Normal intracellular H_2O_2 levels are in the picomolar range[19,21]. Thus, septic blood has over a million times greater H_2O_2 concentration than normal cells resulting in the potential for significant systemic cellular cytotoxicity which can disrupt metabolic pathways and organ function.

Other clinical abnormalities observed in sepsis such as hypotension, coagulopathy, encephalopathy, microangiopathic and cardiac dysfunction, erythrocyte rigidity, methemoglobinemia, glutathione depletion, mitochondrial damage, and lymphocyte apoptosis are also documented adverse effects of H_2O_2, all of which contribute to multiple organ failure and lymphocytopenia observed in sepsis[22-25].

But where does all this H_2O_2 come from? Although leukocytes such as neutrophils can produce large amounts of H_2O_2 during the respiratory burst[26], the profound immunosuppression[7,27-30] during advanced stages of sepsis suggests a significant non-immune contribution to the persistently elevated blood H_2O_2 levels observed in advanced sepsis and septic shock. Significant depletion of tissue glutathione in muscle, lung, and erythrocytes in addition to plasma thiol depletion (albumin cys34) suggests these tissues have become H_2O_2 generators contributing to elevated blood H_2O_2 in sepsis patients[22,31,32].

The production of mitochondrial H_2O_2 depends upon the rate of electron transfer through the ETC. The higher the electron transfer rate the greater the production of H_2O_2. Studies in isolated mitochondria have shown an exponential increase in reactive oxygen species (*i.e.*, H_2O_2) at strongly polarized levels of mitochondrial membrane potential[33], which can occur in hypermetabolic critically ill patients. Other studies in mice have shown that mitochondrial H_2O_2 will increase up to 15x the normal rate during state-3 (maximal) respiration[34]. The clinical correlate of state-3 respiration is a hypermetabolic state, which is characterized by tachycardia, tachypnea, leukocytosis, high fever, and significantly enhanced protein biosynthesis. These are the cardinal elements that define the systemic inflammatory response syndrome (SIRS), which accompanies sepsis. This implies that a clinical hypermetabolic response is accompanied by supraphysiological increases in ETC-generated H_2O_2 and is the common factor linking infectious and non-infectious sepsis.

Due to the limited amount of mitochondrial glutathione available for H_2O_2 neutralization in addition to high basal levels of mitochondrial H_2O_2, a sustained hypermetabolic response can overwhelm cellular reductive (antioxidant) capacity resulting in un-neutralized H_2O_2 leaking out of cells and into the bloodstream with a subsequent rise in blood H_2O_2 reaching toxic levels[35-40].

H_2O_2 is a metabolic poison and the data suggest that sepsis is due to an endogenous H_2O_2 poisoning secondary to the oxidative damage inflicted by this highly toxic oxidizing agent. Since H_2O_2 is permeable through cell membranes, elevated blood H_2O_2 indicates systemic reductive depletion, which perpetuates the production of H_2O_2 [41]. Toxic levels of H_2O_2 will disrupt cellular function in all body organs, which can lead to multiple organ failure and microvascular dysfunction. Any cell undergoing a hypermetabolic response can deplete its reductive capacity and contribute to total body H_2O_2 load.

A potential cause and effect relationship between H_2O_2 and sepsis has likely remained obscure because a hypermetabolic state, which generates H_2O_2, is a confounding factor in the relationship between infection and sepsis (Figure 2)[42-51].

Based on the data, H_2O_2 is also an intervening variable in the setting of critical illness-associated sepsis (Figure 3)[52-55]. Intervening variables have an important role in therapy as they are mechanistically "closer" to the final effect and can serve as a therapeutic target. The observation that culture-positive sepsis patients on appropriate antibiotics still die suggests an additional factor independent of infection that exerts a significant influence on the clinical outcome of sepsis[5]. In this scenario, the H_2O_2 induced tissue damage and metabolic dysfunction (the effect) is too severe and can no longer be reversed by treating the infection (the exposure) with antibiotics. As an intervening variable with a postulated causal role in sepsis, H_2O_2 explains why culture positivity is not independently associated with mortality in sepsis[5] since the data supports H_2O_2 (and not infection per se) as the proximal causal agent in sepsis.

Figure 1 Krebs cycle derived reducing equivalents (NADH, FADH2) donate electrons that are processed by the electron transport chain during oxidative phosphorylation. Up to 5% of electrons (e^-) will normally escape the electron transport chain (ETC) into the mitochondrial matrix (electron leakage)[14-16]. These electrons combine with molecular oxygen (O_2) to form superoxide anion radical (O_2^-), which is metabolized by superoxide dismutase (SOD) to hydrogen peroxide (H_2O_2) that in turn is converted to glutathione disulfide (GS-SG) and water *via* glutathione peroxidase (GPX) and its reducing co-factor glutathione (GSH). Critical illness hypermetabolic states increase ETC activity leading to enhanced electron leakage and far greater H_2O_2 formation, which can deplete cellular GSH resulting in a build-up of H_2O_2 in cells and blood causing bioenergetic dysfunction and organ failure.

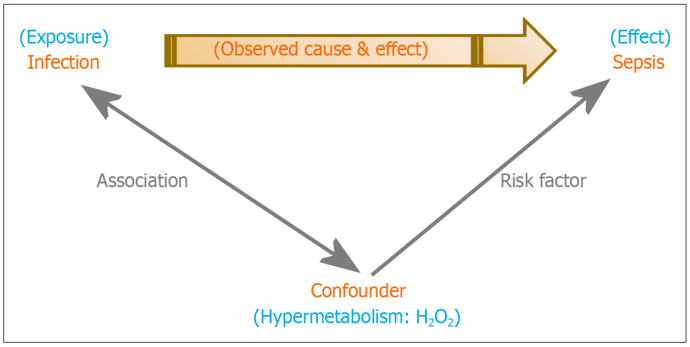

Figure 2 Confounding in Sepsis: The hypermetabolic state that accompanies a critical illness is a con-founding factor in the relationship between systemic infection (exposure) and sepsis (effect). Hypermetabolism generates large amounts of hydrogen peroxide (H_2O_2), which is both a risk factor for the development of sepsis and is bilaterally associated (double arrow) with infection. Systemic infection triggers a hypermetabolic state accompanied by greatly amplified generation of H_2O_2, but non-infectious critical illness can also generate large amounts of H_2O_2 due to the accompanying hypermetabolic state. High levels of blood H_2O_2 can cause systemic lymphocyte apoptosis leading to significant lymphocytopenia, which predisposes to infection. Thus, systemic build-up of H_2O_2 can lead to sepsis. This can occur after an infectious or non-infectious insult. In the latter instance, infection may develop as a result of H_2O_2 induced systemic lymphocyte apoptosis and subsequent lymphocytopenia.

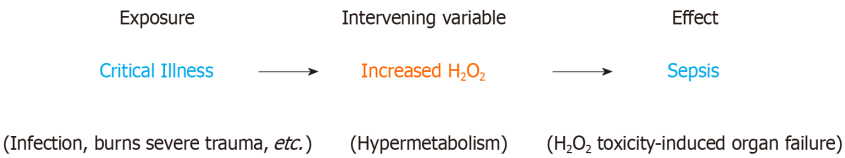

Figure 3 Sepsis and intervening variables: Hydrogen peroxide is an intervening variable between a critical illness (exposure), which triggers a systemic hypermetabolic response, and sepsis (effect). Hypermetabolism, characterized by the systemic inflammatory response syndrome, is the clinical manifestation of supraphysiological cellular H_2O_2 production. This will eventually lead to reductive depletion and sepsis (H_2O_2 toxicity, bioenergetic organ failure) if allowed to persist. Prolonged critical illness (hypermetabolism) and dietary restriction severely limit the body's ability to re-establish and maintain redox homeostasis. Under these circumstances, direct acting reducing equivalents must be supplied to the patient to aid in neutralizing excess H_2O_2. A hypermetabolic response to critical illness or injury may continue for years after hospital discharge and contribute to increased inpatient and post-discharge morbidity and mortality (chronic critical illness and post sepsis syndrome respectively)[52-55].

All hypermetabolic states (infectious and non-infectious), have the potential of generating excess H_2O_2, which can accumulate to toxic levels leading to bioenergetic organ failure and sepsis. The relationship between exposure (infection) and con-founder (H_2O_2) is bilateral because systemic infections cause a hypermetabolic state that can elevate blood H_2O_2 but non-infectious hypermetabolic states (*i.e.*, burns, multiple body trauma) can generate sufficient H_2O_2 leading to generalized lymphocyte apoptosis and profound lymphocytopenia, which can lead to infection. Serial negative blood cultures can eventually turn positive because of this phenomenon. In other words, infections can increase blood H_2O_2 but a primary non-infectious increase in blood H_2O_2 can eventually lead to infection, reinforcing the widely held view that sepsis is always due to infection. In the latter case, infection is the result of H_2O_2 induced lymphocytopenia (Figure 4).

Studies have shown that certain antibiotics can cause mitochondrial dysfunction accompanied by a significant production of H_2O_2[46]. This implies that patients must have sufficient residual reductive capacity to deal with the oxidative stress imposed by antibiotic treatment, underscoring the critical need to begin antibiotics along with

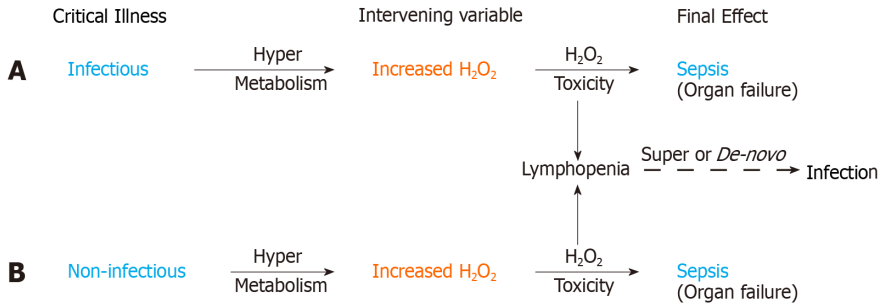

Figure 4 H_2O_2 induced immune system failure. Sequences 4A and 4B illustrate the common hypermetabolic response in infectious and non-infectious critical illness leading to H_2O_2 toxicity induced organ failure and sepsis. Lymphocytes are highly sensitive to H_2O_2 induced apoptosis. Lymphopenia is thus a manifestation of H_2O_2 induced immune system failure secondary to a hypermetabolic response in both infectious and non-infectious critical illness. H_2O_2 induced lymphopenia will predispose to de-novo infection in otherwise sterile critical illness and may cause a super-infection in patients on appropriate antibiotics. H_2O_2 toxicity and/or super-infection may contribute to sepsis mortality despite appropriate antibiotics.

reductive therapy as early as possible during the course of infection-associated sepsis. Reductive therapy encompasses any treatment that increases reductive (antioxidant) capacity, *i.e.*, glutathione, protein thiols, *etc.* The purpose of which (in sepsis) is to augment the patient's reductive (antioxidant) capacity to neutralize H_2O_2.

For the patient, the clinical benefits of limiting exposure to H_2O_2 go beyond discharge from the hospital because H_2O_2 can damage mitochondrial DNA. Mitochondrial DNA (mtDNA) is highly vulnerable to H_2O_2 induced oxidative damage due to the proximity of mtDNA to the electron transport chain, both of which reside on the matrix side of the inner mitochondrial membrane. Exposure of mtDNA to H_2O_2 will inflict base mutations and nucleotide mispairing that upon transcription result in the incorporation of mutated protein subunits into the electron transport chain (ETC). Mutated ETC components interfere with electron transport resulting in augmented electron leakage with increased H^2O^2 generation[47-52]. This establishes a self-amplifying vicious cycle with ever greater production of H_2O_2 and mtDNA damage, which can lead to prolonged metabolic and bioenergetic dysfunction in sepsis survivors and contribute to the post-sepsis syndrome.

H_2O_2 induced impaired redox homeostasis as a primary mechanism of disease is a novel pathogenesis that is supported by experimental evidence and is grounded in fundamental concepts of redox biology, redox biochemistry, and bioenergetics. Similar to electrolyte balance and acid/base buffering systems, redox homeostasis is a vital homeostatic mechanism required for normal cellular function and should be assessed in all critically ill patients.

CLINICAL MANIFESTATIONS OF H2O2 INDUCED OXIDATIVE STRESS

Since most H_2O_2 is a product of mitochondrial electron transport chain activity, clinical manifestations of H_2O_2 begin with its effects on cellular metabolism. Indeed, with almost 40% of all cellular reactions being redox reactions[53], the potential for H_2O_2 induced oxidative impairment of cellular metabolism and bioenergetics cannot be overstated, especially since blood H_2O_2 levels reported in sepsis exceed cellular cytotoxic tolerances by several-fold[17]. The mechanisms of H_2O_2 toxicity mirror the clinical manifestations of sepsis and include:

Hyperlactatemia

Elevated blood lactate is common among patients with sepsis and is associated with significantly greater mortality[12]. Toxic levels of H_2O_2 can inhibit enzymes in the Krebs cycle and electron transport chain leading to hyperlactatemia and bioenergetic failure characteristic of advanced sepsis[54-59]. H_2O_2 increases cellular lactate by interrupting mitochondrial oxidative energy flux (directional oxidation), which is needed to maintain the proton motive force (electrochemical proton gradient) that fuels pyruvate import into the mitochondrial matrix[60,61]. Studies have shown that H_2O_2 inhibits a variety of enzymes including enzymes within the Krebs' cycle such as aconitase, alpha-ketoglutarate dehydrogenase, and Succinate Dehydrogenase[55-57, 62].

Once inhibited, the Krebs cycle can no longer supply sufficient reducing equivalents (NADH, $FADH_2$) needed to sustain the mitochondrial proton gradient. Diminished Krebs cycle supplied reducing equivalents can decrease (and eventually collapse) the mitochondrial proton gradient. This will impair the proton motive force needed for pyruvate translocase in the inner mitochondrial membrane to transport pyruvate into mitochondria in symport with a proton[60,61]. The end result is increased cytosolic pyruvate and subsequent conversion to lactate with resulting hyperlactatemia[11]. Thus, in sepsis, hyperlactatemia can be a manifestation of H_2O_2 toxicity, in which case the reduction of serum lactate alone has no effect on the outcome of sepsis[63,64].

The effect of a dysfunctional Krebs cycle on serum lactate levels can be seen with the inherited deficiency of alpha-ketoglutarate dehydrogenase, which is associated with severe congenital hyperlactatemia[65]. Under these circumstances, increasing inspired oxygen will not lower serum lactate since the problem is with the diminished supply of electrons to the electron transport chain, which collapses the proton gradient dissipating the proton motive force, and not the availability of oxygen.

Studies have shown substantial lactate production from the lungs of patients with septic shock[66]. Hypoperfusion or hypoxia is highly unlikely given that the lungs are continuously bathed in oxygen and receive the entire cardiac output. However, when combined with other studies showing decreased lung glutathione in sepsis, H_2O_2 toxicity is a strong possibility. Therapeutic removal of H_2O_2 (discussed below) can contribute to the normalization of bioenergetic function and serum lactate.

It's worth noting that the mitochondrial proton motive force fuels both ATP synthase and nicotinamide nucleotide transhydrogenase both of which are located in the inner mitochondrial membrane. The former is needed to synthesize ATP while the latter is required to generate mitochondrial NADPH, a critical source of reducing equivalents for the regeneration of mitochondrial glutathione needed to neutralize H_2O_2[13]. Thus, sepsis-associated hyperlactatemia may signal a compromised proton motive force and the start of a vicious cycle leading to increased H_2O_2 induced oxidative stress and bioenergetic failure.

Anemia

A common feature during the progression of sepsis is anemia. Several factors can contribute to the development of sepsis-associated anemia however, sepsis per se is independently associated with the development of anemia, and healthy erythrocytes exposed to plasma from sepsis patients undergo eryptosis[67,68]. H_2O_2 induced oxidative stress initiates erythrocyte suicidal cell death known as eryptosis leading to cell shrinkage and clearance from the blood[68-71]. Thus, H_2O_2 initiated eryptosis may contribute to sepsis-related anemia.

Hypocalcemia

Low serum calcium is a common finding in patients with sepsis and critical illness, with reported prevalence rates of up to 80%[72]. Hypocalcemia may be due to one or more of various causes[73]. However, during sepsis, calcium is shifted into red blood cells with significant increases in erythrocyte calcium of more than twice the control

value[74]. Given that about 85% of all cells in the body are red blood cells, this shift may significantly contribute to sepsis-associated hypocalcemia[75]. Erythrocytes exposed to oxidative stress (*i.e.*, H_2O_2) activate calcium-permeable cation channels leading to calcium entry into the cell[71]. Significantly increased lymphocyte calcium has also been reported in sepsis[76]. This suggests that the elevated blood H_2O_2 reported in sepsis may cause a more generalize intracellular shift of calcium.

Shock

Sepsis-associated hemodynamic instability can progress to septic shock, which carries a high mortality. Oxidative stress due to H_2O_2 exposure causes extensive cytoskeletal disruption to endothelial cells leading to significant endothelial retraction and microangiopathic dysfunction[22]. The net effect of microvascular H_2O_2 exposure is microangiopathic dysfunction, impaired vasomotor responsiveness, barrier disruption with edema formation, and irreversible hypotension (septic shock)[22,77]. Studies have reported hypotension in an animal model after intravenous administration of H_2O_2 [25].

Immunosuppression

Sepsis patients develop profound immunosuppression that begins within days after the onset of sepsis[7,28,30]. Lymphocytes are extremely sensitive to H_2O_2 induced apoptosis, which occurs at H_2O_2 concentrations of less than 1 μmol/L[19,20]. Studies report blood H_2O_2 concentrations in sepsis of up to 558 μmol/L, which is over 500 times the concentration of H_2O_2 needed to cause lymphocyte apoptosis[17-19]. The ability of high blood H_2O_2 concentrations to cause generalized lymphocyte apoptosis explains the profound immunosuppression observed in sepsis patients.

Respiratory failure

Sepsis-associated acute respiratory distress syndrome (ARDS) is a serious complication of sepsis that carries a high mortality. It is characterized by increased permeability of pulmonary capillary endothelial and epithelial cells. The increased vascular permeability leads to diffuse capillary leak, pulmonary edema, and eventual wet lung, which triggers the secondary development of pathological features[78,79]. Studies have demonstrated that low dose H_2O_2 can increase pulmonary vascular bed permeability and capillary filtration[80-83]. This suggests that the high levels of H_2O_2 reported in the blood of sepsis patients may have a causal role in the initiation of ARDS.

Acute kidney injury

Sepsis-associated acute kidney injury (S-AKI) is a life-threatening complication that develops in up to two-thirds of patients with sepsis or septic shock, which in half of the patients develops before seeking medical attention[84]. Once thought to be a consequence of cellular hypoxia leading to acute tubular necrosis, it is now recognized that S-AKI can occur in the setting of normal or increased renal blood flow[84]. Studies suggest a critical role for microcirculatory dysfunction, which is present in every vital organ in animal models and humans with sepsis[84-86]. When combined with studies showing a decreased substrate flux through the Krebs cycle in mice kidneys after the induction of experimental sepsis[87], these effects mirror the known toxic effects of H_2O_2, among which is microangiopathic dysfunction and Krebs cycle enzymatic inhibition[22]. In support of a role for H_2O_2 in S-AKI, studies of experimental murine sepsis employing Mito-TEMPO, a mitochondrially targeted reducing agent (antioxidant) active against H_2O_2, significantly increased renal microcirculation, glomerular filtration rate, and ATP synthesis[88,89].

The renal endothelium is highly vulnerable to oxidative stress with agents such as H_2O_2, a highly toxic oxidizing agent that can diffuse across cell membranes to impair critical signaling and regulatory function required for microvascular function[90]. Other studies report significant cytotoxicity in human tubular epithelial cells exposed to 100 μmol/L H_2O_2, while 200 μmol/L exposure caused mitochondrial cytochrome-C translocation to the cytoplasm in addition to significant intracellular increases in H_2O_2. These concentrations are within the range reported for blood H_2O_2 in sepsis patients of up to 558 μmol/L[17,91]. H_2O_2 can inhibit various enzymes involved in oxidative metabolism including Krebs cycle enzymes, ATP synthase, and nucleotide (ADP-ATP) translocase[55-57,92]. The resulting inhibition in mitochondrial oxidative flux may contribute to the increased glycolytic production of lactate by proximal tubule cells observed during sepsis[93]. Increased glycolysis would revert to oxidative phosphorylation when H_2O_2 induced inhibition of mitochondrial oxidative metabolism

is resolved. Lastly, rat renal artery infusion of 70 mmol/L H_2O_2 (140x that found in human sepsis blood) is reported to cause massive proteinuria without electron microscopic ultrastructural glomerular abnormalities[94]. This is consistent with the minimal postmortem histological findings in human S-AKI[84,86]. This suggests that renal exposure to blood H_2O_2 levels observed in human sepsis may cause cellular dysfunction without overt signs of cellular damage.

Coagulopathy

Disseminated intravascular coagulation (DIC) is a life-threatening complication frequently encountered in sepsis that is characterized by the systemic activation of the coagulation system leading to microvascular thrombosis, and potentially life-threatening hemorrhage due to consumption of platelets and coagulation factors[95]. DIC can originate from damage to the microvasculature, which triggers the extrinsic coagulation cascade[96]. H_2O_2 can cause microvascular injury by peroxidation of endothelial cell membranes, which triggers the expression of tissue factor and subsequent systemic activation of the extrinsic coagulation pathway leading to DIC [97-99]. Intravenous administration of H_2O_2 is reported to have resulted in fatal sepsis and DIC, underscoring the role of H_2O_2 induced oxidative stress in both of these conditions[100].

On a more fundamental level, the endothelium is critically involved in preventing inappropriate coagulation by maintaining barrier function and producing several endogenous anticoagulants[101]. The elevated levels of blood H_2O_2 reported in sepsis can permeate endothelial cells throughout the body causing substantial oxidative stress accompanied by profound disruption in both form and function[77,102]. Studies have reported significant endothelial dysfunction that is associated with mortality and severity of coagulopathy[101]. H_2O_2 induced endothelial dysfunction can explain why anticoagulants fail to show a survival benefit in sepsis-induced DIC[103] since these agents fail to restore endothelial redox homeostasis.

Encephalopathy

Sepsis-associated encephalopathy (SAE) is a diffuse cerebral dysfunction ranging from lethargy and lack of concentration to personality changes, delirium, and coma that occurs secondary to sepsis in the absence of direct central nervous system (CNS) infection. SAE affects up to 70% of sepsis patients and is associated with higher mortality and poorer long term outcomes with half of surviving patients suffering from long-term cognitive defects[104,105]. The brain is highly sensitive to H_2O_2 induced oxidative damage and dysfunction, and studies report dose-dependent cytotoxicity starting at H_2O_2 exposures of 10 μmol/L[106]. Encephalopathy is reported to occur after the accidental ingestion of H_2O_2[107]. Encephalopathy was also reported after intravenous administration of H_2O_2 for alternative medicine therapy[100].

H_2O_2 is diffusible through cell membranes which facilitates its diffusion into the central nervous system where it can disrupt neuronal and synaptic function. Studies have shown that H_2O_2 can alter neuron membrane properties and impair synaptic transmission leading to hyperexcitability and epileptiform activity[108,109]. This is notable because epileptic seizures can be a manifestation of SAE. Other studies have demonstrated bioenergetic impairment with decreased ATP biosynthesis and utilization in neurons exposed to H_2O_2[110,111]. H_2O_2 has also been reported to alter rat hippocampal synaptic plasticity, which can negatively impact long-term potentiation, learning, and memory[112]. Thus, the presence of elevated levels of blood H_2O_2 in sepsis can have acute and chronic effects on brain function and cognition.

TREATMENT

Sepsis is a life-threatening medical emergency that can precipitously evolve into hemodynamic instability, septic shock, and death. Thus it may not be possible or prudent to wait for a blood H_2O_2 level if clinical signs of H_2O_2 toxicity are present. Additionally, it takes some time before free H_2O_2 can accumulate in the bloodstream given the multiple layers of reductive (antioxidant) defense systems that mitochondrial H_2O_2 must traverse on its way to the intravascular compartment including mitochondrial and cytoplasmic glutathione followed by interstitial albumin whose cys34 amino acid can react with H_2O_2 (60% of total albumin) and ultimately serum albumin (40% of total albumin) and red blood cell reductive (glutathione) capacity [13]. During the time it takes to reach the blood stream and build-up, toxic levels of

intracellular H_2O_2 can inhibit critical cellular bioenergetic reactions leading to compromised bioenergetic function. This was demonstrated in ulcerative colitis, an inflammatory bowel disease, in which a primary increase in colonic epithelial H_2O_2, thought to have a causal role in this disease, resulted in impaired beta-oxidation due to H_2O_2 inhibition of mitochondrial thiolase, the last enzyme in the beta-oxidation cascade[113].

Within this context, the data support the critical need for reduction of systemic H_2O_2 in sepsis to prevent bioenergetic organ failure and restore microcirculatory function. Restoration of redox homeostasis by the elimination of excess H_2O_2 must accompany other therapeutic interventions to optimize clinical responsiveness and outcome. Sodium thiosulfate (STS) is a direct-acting reducing agent that can neutralize H_2O_2 upon contact.

STS is approved for use in cyanide poisoning with a recommended dose of 12.5 g over slow IV infusion (10 to 20 min) in adults and 250 mg/kg in children[114]. Similar dosing regimens can be considered in sepsis. Repeat dosing can be guided by clinical status, blood reducing capacity (glutathione, plasma thiols), and blood H_2O_2 levels. The general chemical reaction for the reduction of H_2O_2 with sodium thiosulfate yields sodium trithionate, sodium sulfate, and water[115].

$2Na_2S_2O_3 + 4H_2O_2 \rightarrow Na_2S_3O_6 + Na_2SO_4 + 4H_2O$

The rationale underlying STS administration in sepsis is to reduce blood H_2O_2 to normal (less than 30 μmol/L) in order to allow intracellular H_2O_2 to diffuse down its concentration gradient into the systemic circulation where it can be neutralized by STS. STS is generally well tolerated and is an accepted therapy for cisplatin toxicity and renal failure associated calciphylaxis (25 g three times weekly)[116,117]. High dose STS (up to 16 g per M^2 surface area, repeated after 4 h) is reported to be well tolerated in children under 12 years of age[118].

STS is reported to replenish intracellular glutathione, which will aid in the removal of intracellular H_2O_2 and restoration of redox homeostasis[119,120]. Decreasing serum lactate indicates that H_2O_2-induced Krebs cycle inhibition and bioenergetic dysfunction are being reversed. Restoration of vascular responsiveness by STS may cause extant vasopressor measures to have an unanticipated amplified effect. Thus, STS administration in critically ill patients should be accompanied by close patient monitoring. Finally, if STS therapy proves to be successful in the treatment of sepsis then treatment with STS should be considered in all critically ill (hypermetabolic) patients in order to restore depleted systemic reducing equivalents before blood H_2O_2 becomes toxically elevated.

Specific treatment considerations

ARDS: Inhaled STS may have a beneficial effect to neutralize H_2O_2 that has diffused through the alveolar-capillary membrane causing oxidant damage in the alveolar space.

S-AKI: Primary prevention of S-AKI is not possible in all patients because most patients developing S-AKI already have it at presentation. Administration of STS should be considered when patients first seek medical care to initiate primary or secondary prevention.

The evidence supports the use of STS as a specific therapeutic agent for the treatment of sepsis and its associated complications. Given the high mortality, significant societal burden, and absence of a safe and effective treatment for this deadly condition, clinical studies are urgently needed to determine the effectiveness of STS for the treatment of sepsis.

CONCLUSION

The mortality in sepsis is unacceptably high because there is no specific therapy to treat the sepsis syndrome. H_2O_2 toxicity mirrors the clinical and laboratory abnormalities observed in sepsis, and toxic levels of blood H_2O_2 have been reported in this condition. This and other data implicate H_2O_2 as the causal factor in the pathogenesis of sepsis, which predictably develops accompanied by systemic depletion of reducing equivalents (*i.e.*, glutathione) needed for the reduction (neutralization) of metabolically generated H_2O_2. Once the body's reductive (antioxidant) capacity is depleted, H_2O_2 will continue to be generated and flood the system.

Prolonged supraphysiological production of H_2O_2 generated by electron transport chain hyperactivity during a hypermetabolic state (such as sepsis) can overwhelm

cellular reductive systems leading to H_2O_2 accumulation within tissues and blood. H_2O_2 is a highly toxic membrane-permeable metabolic poison that can cause severe bioenergetic dysfunction and cellular damage if allowed to accumulate. Continued exposure can lead to the collapse of systemic redox homeostasis, proton motive force dissipation, organ failure, microvascular dysfunction, and fatal septic shock. Reduction of blood H_2O_2 is paramount in order to prevent H_2O_2 toxicity from irreversibly shutting down cellular metabolism.

The data support the use of sodium thiosulfate as a systemic reducing agent with the goal of restoring redox homeostasis by neutralizing excess systemic H_2O_2. Prophylactic use of sodium thiosulfate in all critically ill (hypermetabolic) patients should be considered before irreversible H_2O_2 induced bioenergetic failure and microvascular dysfunction develop.

Based on the data, the missing critical intervention to improve patient outcomes and reduce mortality in patients with sepsis and septic shock is the normalization of systemic redox homeostasis. The addition of specialists in redox medicine to the team providing care to critically ill patients can contribute to achieving this heretofore elusive goal.

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