

Hypothesis

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Hypothesis

Combined Glucose and Thiamine Treatment for Sepsis

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Abstract

Sepsis is usually described as a dysregulated host response to infection associated with severe organ dysfunction and failure. In 2023 the author proposed that many aspects of sepsis suggested a physiological response and defence to infection that only became “dysregulated” if the infection was overwhelming or there was a deficiency of thiamine and/or intracellular glucose to provide ongoing fuel for the immune response and/or mitochondrial production of adenosine triphosphate (ATP). It was also proposed that during sepsis, the immune system received priority access to available glucose, prompting insulin resistance that minimised glucose utilisation by less essential tissues. Concurrently, mitochondrial ATP production via oxidative phosphorylation (OXPHOS) was deprioritised, with the immune system relying on anaerobic glycolysis for ATP generation. This suppression of OXPHOS was only a temporary measure; mitochondrial ATP production had to be resumed for complete recovery. Persistent suppression culminated in critical ATP deficits and cell death. The 2023 paper also reviewed glucose, thiamine and insulin metabolism during sepsis and concluded that administering high-dose insulin alongside mild hyperglycaemia and intravenous thiamine—a pyruvate dehydrogenase kinase (PDK) inhibitor—might help restore physiological mitochondrial ATP production when administered during a critical window in the sepsis process, potentially improving survival outcomes. The thrust of that hypothesis may have been validated by a recent experiment on sepsis in mice that found superior survival, albeit short term, following treatment with combined glucose and thiamine compared to antibiotics.

Keywords: sepsis; mitochondria; adenosine triphosphate; ATP; pyruvate dehydrogenase complex; PDHC; thiamine; glycolysis; glucose; insulin; lipopolysaccharides; LPS; oxidative phosphorylation; OXPHOS; pyruvate dehydrogenase kinase; PDK; lactate

Introduction

Sepsis is responsible for 20% of global deaths and ranks as the costliest condition in United States hospitals, averaging approximately \$46,000 per patient. Despite this, treatment options remain largely supportive, with hospitalised patient mortality at around 27% and intensive care patient mortality reaching 42%. It is claimed that sepsis was responsible for most deaths during the COVID-19 pandemic [1]. Notably, mortality rates in the United States remained static between 1999 and 2022 [2]. While early recognition is thought to enhance survival, the evidence underpinning Early Warning Scores (EWS) is limited [3].

Health costs do not end with the acute phase of sepsis. Prior sepsis is the most common reason for 30-day unplanned rehospitalization with healthcare costs exceeding diseases such as acute myocardial infarction, chronic obstructive pulmonary disease, heart failure and pneumonia [1]. 31.5% Of survivors rely on nursing care for 3 years after discharge and the healthcare burden of these global survivors is \$ billions per year [4].

Is Sepsis a Dysregulated Response to Infection?

Sepsis is usually described as a life-threatening disorder caused by a dysregulated host response to infection associated with organ dysfunction.

However, rather than being dysregulated many aspects of sepsis indicate a highly regulated response and defence against invading microorganisms that represents millions of years of evolution honing the body's defences against invading organisms.

Prior to the advent of antibiotics this was the organism's only defence and it was relatively successful. For example, survival from uncomplicated pneumococcal pneumonia was 70% [5]. The spleen also illustrates the effectiveness of these immune defences because of its role in leukocyte production, antibody production, phagocytic filtering out of bacteria and opsonizing bacteria. Thus, splenectomy significantly increases the risk of death from infections, and the mortality rate can be as high as 70% and occur under 24 hours in overwhelming post-splenectomy infections [6].

This process becomes "dysregulated" particularly under two circumstances – overwhelming infection and deficiencies of thiamine and/or intracellular glucose to provide ongoing fuel for the immune system and/or OXPHOS. Glucose inadequacy is also a prominent cause of death in premature infants because of the heightened risk of hypoglycaemia.

Sepsis as a Physiological Response to Infection

The hypermetabolic phase of sepsis represents this defensive process. Leucocyte numbers surge and migrate to sites of infection and tissue injury. Immune activation during sepsis is an energy intensive process and raises metabolic rates by 37–55%. Glucose consumption increases to fuel this increased demand and glucose production increases to meet this. Insulin resistance reduces glucose uptake by less essential organs, while the liver boosts glucose output and the kidneys increase glucose reabsorption. Adipose tissue releases more free fatty acids and glycerol, which are used as alternative fuels or substrates for hepatic glucose production. Skeletal muscle is catabolised to supply amino acids for gluconeogenesis [7,8]. In severe infections such as malaria, hepatic glucose output can double from 200 to 400 g/day [9,10].

Due to lower glycogen reserves than those found in adults, children are especially vulnerable to severe hypoglycaemia because of this diversion of available glucose, increasing mortality by four- to sixfold compared to those without hypoglycaemia [9,10].

For immune cells in particular, anaerobic glycolysis becomes the dominant ATP-producing pathway, due to its capability of generating ATP 100 times faster than OXPHOS. It additionally functions effectively under anaerobic or ischaemic conditions that are characteristic of infected or damaged tissues. Other organs, including the kidneys and heart, also partially switch to glycolysis for ATP production [8]. Unlike exercise-induced rises in lactate, which do not suppress OXPHOS or increase morbidity [11], sepsis-related lactate elevations are linked to high mortality [12].

In healthy organisms, 95% of cellular ATP is produced via mitochondrial OXPHOS, amounting to 100–150 moles or 25–40 kg per day [8].

Experimental studies on, for example Holstein cows, illuminate this sequence of metabolic events. The administration of lipopolysaccharide (LPS)—a component of gram-negative bacterial membranes—caused serum glucose levels to spike from 60 mg/dL (4 mmol/l) to 155 mg/dL (9 mmol/l) within 30 minutes, indicating acute insulin resistance. Subsequently, glucose levels dropped to a deficiency level at 30 mg/dL (2 mmol/l) due to increased immune demand, necessitating glucose infusion to maintain euglycemia. This diversion of glucose to the immune system, away from tissues such as the mammary glands—which exhibited an 80% reduction in milk production—demonstrates the body's prioritisation of immune function during perceived threats, even in the absence of live microbes [13].

In further imaging studies using radiolabelled glucose and positron emission tomography in Dutch dwarf rabbits researchers demonstrated a marked reduction in glucose uptake by most organs after LPS administration because of the diversion of glucose to the immune system, featuring

increased renal glucose uptake also to support the immune system. This diversion leads to hypothermia, as limited glucose availability curtails less critical functions like thermogenesis [14].

Another critical change during sepsis is the inhibition of the mitochondrial pyruvate dehydrogenase complex (PDHC), driven by increased PDK enzyme activity. This suppression of mitochondrial ATP production is corroborated by proteome analyses, demonstrating elevated PDK and reduced PDHC levels during sepsis [7,8].

The Hypometabolic Phase of Sepsis

Even the early phases of the hypometabolic phase of sepsis suggests adaptation rather than dysregulation particularly the reduced metabolic activity akin to hibernation as a response to the high demand for glucose in the presence of a deficiency of intracellular glucose.

While glycolysis can rapidly supply ATP, it is insufficient for the ongoing energy needs of the entire organism. Its role is primarily to meet the urgent ATP demands of immune cells operating in low-oxygen or ischaemic environments [7,8]. This limitation is evident in sepsis-induced cardiac dysfunction, as the organ with the highest mitochondrial density, the heart depends on continual ATP supply and mitochondrial dysfunction is central to septic cardiomyopathy [15].

Non-surviving septic patients exhibit elevated respiratory capacity but reduced mitochondrial respiration associated with ATP synthesis, whereas survivors show increased mitochondrial activity during recovery [7]. A direct correlation exists between mortality and patient body temperature upon admission to the emergency department; those with temperatures below 35°C exhibit a 48% 30-day mortality rate, compared to 11% for those above 41°C [16]. The generation of fever requires uncoupled mitochondrial respiration [17], yet the inhibition of mitochondrial function suppresses fever [18].

The hypometabolic phase is characterised by decreased oxygen consumption (VO₂) and basal metabolic rate in spite of, a high respiratory capacity and poor response to increased systemic oxygen. Multi-organ dysfunction syndrome (MODS) is a prominent feature, marked by minimal cell death, reduced substrate consumption, and normal or elevated tissue oxygen levels. MODS may represent an adaptive strategy to minimise energy requirements, like hibernation [8,19]. Even sepsis-induced cardiac dysfunction may reflect functional, adaptive changes to reduce oxygen and ATP consumption [20]. During recovery, hospital survivors show a 50–60% increase in systemic VO₂ and resting metabolic rate, consistent with renewed mitochondrial ATP production [18].

Intracellular Glucose Availability

Glucose availability is a key factor influencing both the risk of developing sepsis and subsequent mortality. Neonates, particularly those born preterm, are at increased risk due to limited glycogen and fat stores, as well as low gluconeogenic enzyme expression, and high glucose requirements for their larger brain. Unable to adequately respond to hypoglycaemia, up to 60% require supplementary glucose to prevent morbidity and long-term complications [21], and they are more susceptible to sepsis and sepsis-related death [22,23].

Children aged 5–14 exhibit significantly lower sepsis-related mortality than adults, even with similar infection rates. This phenomenon has been observed in events such as the 1918 flu pandemic (as well as in other infectious diseases), and it is likely linked to higher glucose availability [24]. Children have three times the normalised glucose production of adults [25,26] in addition to lower insulin resistance, reflecting greater glucose surplus [27,28].

Data also indicates that patients with hyperthermia are more likely to survive sepsis than those with hypothermia [16]. Glucose is the primary fuel for the activated immune system; therefore those able to maintain elevated body temperatures during infection have surplus glucose beyond immune needs, whereas those with marginal glucose reserves may lack sufficient fuel for thermogenesis, resulting in hypothermia. Mechanically ventilated septic patients warmed with forced-air blankets for 48 hours experienced a 25% reduction in 28-day mortality [29].

Addressing the controversial issue of the optimal range of blood glucose (BG) in sepsis a study reviewed BG trajectories during the first 48 hours after intensive care unit (ICU) admission and their relationship to 1-year mortality. The optimal range associated with the lowest mortality was found to be between 122 mg/dl and 160 mg/dl. The increased mortality associated with lower ranges was attributed to hypoglycaemia. The increased mortality associated with higher ranges was attributed to oxidative stress, coagulation activation and endothelial dysfunction [30]. However, hyperglycaemia may reflect impaired glucose transport into the intracellular cytoplasm because of insulin resistance. Thus, the toxic factor may not be hyperglycaemia per se but deficient intracellular glucose availability.

Insulin

Insulin availability similarly impacts sepsis risk and outcomes. The heart, with the highest ATP consumption of any organ, is particularly sensitive to ATP availability. Patients with chronic heart failure often exhibit elevated insulin resistance, and low insulin levels are associated with increased mortality [31]. Studies utilising animal models have demonstrated that insulin administration improves cardiac output, oxygen delivery, and vascular resistance following LPS challenge [32].

Mitochondrial protein synthesis is vital for cellular function and increases only when essential amino acids are infused alongside high insulin concentrations [33]. Glucose is a major myocardial fuel, especially under low-oxygen or ischaemic conditions, and insulin orchestrates glucose uptake, glycolysis, and mitochondrial oxidation, directly enhancing ATP production [34].

Acute kidney injury (AKI) affects over 40% of septic patients; this is further exacerbated by mitochondrial dysfunction due to the presence of excessive reactive oxygen species (ROS), ATP depletion, and membrane potential disruption. Insulin therapy mitigates mitochondrial damage, reverses ATP depletion, reduces oxidant production, improves antioxidant levels, and suppresses renal mitophagy [35].

In septic patients, elevated insulin concentrations increase glucose uptake and oxidation [36]. In animal studies, high-dose insulin (HDI) was shown to improve survival rates during septic shock [37]. In mice particularly, LPS administration raised insulin levels without altering blood glucose, but blocking insulin secretion resulted in severe hyperglycaemia and increased mortality. Non-survivors exhibited significantly lower insulin levels compared to survivors [38]. In paediatric burn patients, intensive insulin therapy decreased infection and sepsis incidence, in addition to alleviating insulin resistance, reducing catabolism, and lowering mortality [39]. Moreover, insulin enhanced survival and reduced positive blood cultures in rodent models of burn wound infection [40].

Glucose and Insulin

Independently, increased availabilities of both glucose and insulin improve sepsis survival, an effect compounded by their combination. In vitro, cardiomyocytes exposed to simulated ischemia showed up to 75% greater ATP production and 40% less lactate when treated with glucose and insulin, reducing cellular injury [41]. Septic rats treated to maintain blood glucose between 8–10 mmol/L displayed superior glucose utilisation and increased expression of the glucose transporter GLUT4 [42].

A large proportion of morbidity and mortality from septic shock stems from refractory hypotension and cardiovascular collapse; thus, counteracting these effects may improve outcomes. Administration of glucose-insulin-potassium (GIK) to patients with severe sepsis and septic shock improved mean arterial pressure and reduced heart rate in those with hypodynamic myocardial depression. The total insulin dose correlated with haemodynamic improvement [43].

The Pyruvate Dehydrogenase Complex

Restoring mitochondrial ATP production during sepsis faces two barriers: severe insulin resistance and suppression of PDHC. High-dose insulin can address the former, increasing

intracellular glucose. The latter, which inhibits pyruvate transfer into mitochondria, is mediated by PDK enzymes. Glycolysis produces ATP by converting glucose to pyruvate and lactate in the cytoplasm (yielding two ATP units). Under aerobic conditions, pyruvate enters mitochondria and is oxidised to acetyl-CoA via PDHC, producing 36 ATP units. PDHC is suppressed in sepsis, but PDK activity can be inhibited by agents such as dichloroacetate (DCA), thiamine, amrinone, TNF-binding protein, and ciprofloxacin, each enhancing mitochondrial pyruvate uptake and ATP generation [44].

Changes in PDHC activity are not limited to immune cells; sepsis-induced cardiomyopathy—a major cause of death—correlates with increased PDK4 levels and PDHC inhibition [45]. PDK inhibitors also rebalance metabolic and transcriptional responses in liver cells during the low-energy, anti-inflammatory phase of sepsis [46].

Thiamine

Thiamine, a vitamin and PDK inhibitor, is linked to improved clinical outcomes in sepsis. A review of over 11,500 Sepsis-3 patients found that intravenous thiamine reduced 28-day mortality and the risk of myocardial infarction [47]. However, clinical trials of thiamine supplementation have yielded mixed results, potentially due to differences in dosage, administration route, timing, duration, sample size, septic phenotype, and medication combinations as well as the presence or absence of deficiency. Some trials have shown positive effects, particularly in patients with severe pneumonia [48], while others have found no benefit in septic shock [49].

Treatment with a Combination of Thiamine and Glucose

A recent study evaluated the impact of combined thiamine and glucose treatment for sepsis.

A cecal ligation and puncture (CLP) model of mouse sepsis evaluated antibiotics, thiamine and glucose [12]. All four groups of animals were administered antibiotics (Ceftriaxone and metronidazole administered intraperitoneally). One group was also administered glucose; the second was also administered thiamine; and the third group was administered a combination of glucose and thiamine. The fourth group was administered the antibiotics only.

In the group treated with combined thiamine, glucose and antibiotics survival at 100 hours was 90% whereas survival of the group at 100 hours that was treated only with antibiotics was only 10%. While this was a short-term outcome it is the first possible validation of the thrust of a paper published in 2023 by the author proposing thiamine plus glucose treatment for sepsis [50].

The addition of insulin will further enhance survival particularly longer-term survival because insulin counteracts insulin resistance and thereby enhances glucose transfer into the intracellular cytoplasm. An important element for inhibiting the sepsis process is intracellular glucose availability because this is a key precursor to mitochondrial ATP production.

Conclusion

High-dose insulin combined with mild hyperglycaemia and PDK inhibitors such as intravenous thiamine act on distinct enzymatic pathways, overcoming barriers to mitochondrial ATP production. This combination, if administered during a critical window in the sepsis process, may significantly enhance survival from sepsis.

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