Hypothesis



# Glucose Metabolism – The Key to Sepsis

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# Glucose Metabolism: The Key to Sepsis

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**Abstract**

Sepsis initiates two primary metabolic responses: insulin resistance in insulin-responsive tissues and suppression of mitochondrial adenosine triphosphate (ATP) production. These mechanisms underpin the hypermetabolic and hypometabolic phases of sepsis. The hypermetabolic phase features a heightened metabolic rate, rapid immune activation, and increased glucose supply and consumption. In contrast, the hypometabolic phase involves a reduction in metabolic rate and physiological activity across multiple organs, mirroring hibernation-like states. During sepsis, the immune system receives priority access to available glucose, prompting insulin resistance that minimises glucose utilisation by less essential tissues. Concurrently, mitochondrial ATP production via oxidative phosphorylation (OXPHOS) is deprioritised, with the immune system relying on anaerobic glycolysis for ATP generation. This suppression of OXPHOS is only a temporary measure; mitochondrial ATP production must resume for complete recovery. Persistent suppression of mitochondrial ATP production can culminate in critical ATP deficits and cell death. This review examines glucose and insulin metabolism in sepsis, concluding that administering high-dose insulin alongside mild hyperglycaemia and intravenous thiamine—a pyruvate dehydrogenase kinase (PDK) inhibitor—may help restore physiological mitochondrial ATP production during a crucial window in the sepsis process, potentially improving survival outcomes. Additionally, by illustrating that antibiotics have no impact on the course of the established sepsis process this may minimise excessive antibiotic usage.

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

## 1. 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%. Notably, mortality rates in the United States remained static between 1999 and 2022 [1]. While early recognition is thought to enhance survival, the evidence underpinning Early Warning Scores (EWS) is limited [2].

Experimental studies, such as those with Holstein cows, have illuminated the sequence of metabolic events during sepsis. 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 (10 mmol/l) within 30 minutes, indicating acute insulin resistance. Subsequently, glucose levels dropped to a deficiency 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 like the mammary glands—which exhibited an 80% reduction in milk production—demonstrates the body's prioritisation of immune function during perceived threats, even without live microbes [3].

Further imaging studies using radiolabelled glucose and positron emission tomography in Dutch dwarf rabbits have shown a marked reduction in glucose uptake by most organs after LPS

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administration, with increased renal glucose uptake to support the immune system. This diversion leads to hypothermia, as limited glucose availability curtails less critical functions like thermogenesis [4].

Another critical change during sepsis is the inhibition of the mitochondrial pyruvate dehydrogenase complex (PDHC), driven by increased activity of PDK enzymes. This suppression of mitochondrial ATP production is corroborated by proteome analyses, which demonstrate elevated PDK and reduced PDHC levels during sepsis [5,6].

## 2. The Hypermetabolic Phase of Sepsis

Immune activation during sepsis raises metabolic rates by 37–55%. Leucocyte numbers surge and migrate to sites of infection and tissue injury. 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, and ATP production via OXPHOS is suppressed [5,6].

In severe infections like malaria, hepatic glucose output can double from 200 to 400 g/day. Children, who have lower glycogen reserves than adults, are especially vulnerable to severe hypoglycaemia, which can increase mortality four to sixfold compared to children without hypoglycaemia [7,8].

Anaerobic glycolysis becomes the preferred ATP-producing pathway, particularly for immune cells, as it is capable of generating ATP 100 times faster than OXPHOS and functions effectively under anaerobic or ischaemic conditions characteristic of infected or damaged tissues. Other organs, including the kidneys and heart, also partially switch to glycolysis for ATP production. Unlike exercise-induced rises in lactate, which do not suppress OXPHOS or increase morbidity [9], sepsis-related lactate elevations are linked to high mortality [10].

In healthy organisms, 95% of cellular ATP is produced via mitochondrial OXPHOS, amounting to 100–150 moles or 25–40 kg per day [6].

## 3. The Hypometabolic Phase of Sepsis

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 [5,6]. This limitation is evident in sepsis-induced cardiac dysfunction, as the heart depends on continual ATP supply and mitochondrial dysfunction is central to septic cardiomyopathy, an organ with the highest mitochondrial density [11].

Non-surviving septic patients exhibit elevated respiratory capacity but reduced mitochondrial respiration associated with ATP synthesis, while survivors show increased mitochondrial activity during recovery [5]. There is a direct correlation between body temperature at emergency department admission and mortality: patients with temperatures below 35 °C have a 48% 30-day mortality rate, compared to 11% for those above 41 °C [12]. The generation of fever requires uncoupled mitochondrial respiration [13], and inhibition of mitochondrial function suppresses fever [14].

The hypometabolic phase is characterised by decreased oxygen consumption (VO2) and basal metabolic rate, despite 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, similar to hibernation [6,15]. Even sepsis-induced cardiac dysfunction may reflect functional, adaptive changes to reduce oxygen and ATP consumption 16]. During recovery, hospital survivors show a 50–60% increase in systemic VO2 and resting metabolic rate, consistent with renewed mitochondrial ATP production [14].

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## 4. Hyperglycaemia

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, 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 [17], and they are more susceptible to sepsis and sepsis-related death [18,19].

Children aged 5–14 exhibit significantly lower sepsis-related mortality than adults, even when infection rates are similar. This phenomenon, observed in events like the 1918 flu pandemic and other infectious diseases, is likely linked to higher glucose availability [20]. Children have three times the normalised glucose production of adults [21,22] and lower insulin resistance, reflecting greater glucose surplus [23,24].

Data also indicate that patients with hyperthermia are more likely to survive sepsis than those with hypothermia [12]. Since glucose is the primary fuel for the activated immune system, 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 [25].

## 5. Hyperinsulinemia

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 [26]. Studies in animal models have shown that insulin administration improves cardiac output, oxygen delivery, and vascular resistance following LPS challenge [27].

Mitochondrial protein synthesis is vital for cellular function and increases only when essential amino acids are infused alongside high insulin concentrations [28]. 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 [29].

Acute kidney injury (AKI) affects over 40% of septic patients, with mitochondrial dysfunction contributing through 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 [30].

Elevated insulin concentrations in septic patients increase glucose uptake and oxidation [31]. In animal studies, high-dose insulin (HDI) improved survival rates during septic shock [32]. In mice, LPS administration raised insulin levels without altering blood glucose, but blocking insulin secretion resulted in severe hyperglycaemia and increased mortality. Non-survivors had significantly lower insulin levels compared to survivors [33]. In paediatric burn patients, intensive insulin therapy decreased infection and sepsis incidence, alleviated insulin resistance, reduced catabolism, and lowered mortality [34]. Insulin also enhanced survival and reduced positive blood cultures in rodent models of burn wound infection [35].

## 6. Glucose Plus Insulin

Both increased glucose and insulin availability individually improve sepsis survival, and their combination has a compounded effect. 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 [36]. Septic rats treated to maintain blood glucose between 8–10 mmol/L displayed superior glucose utilisation and increased expression of glucose transporter GLUT4 [37].

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Much morbidity and mortality from septic shock stem 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 [38].

## 7. The Pyruvate Dehydrogenase Complex

Restoring mitochondrial ATP production during sepsis requires overcoming two barriers: severe insulin resistance and suppression of PDHC. High-dose insulin can address insulin resistance, increasing intracellular glucose. Suppression of PDHC, 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 [39].

PDHC activity changes are not limited to immune cells; sepsis-induced cardiomyopathy—a major cause of death—correlates with increased PDK4 levels and PDHC inhibition [40]. PDK inhibitors also rebalance metabolic and transcriptional responses in liver cells during the low-energy, anti-inflammatory phase of sepsis [41].

## 8. 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 [42]. However, clinical trials of thiamine supplementation have yielded mixed results, potentially due to differences in dosage, administration route, timing, presence or absence of deficiency, duration, sample size, septic phenotype, and medication combinations. Some trials have shown positive effects, particularly in patients with severe pneumonia [43], while others have found no benefit in septic shock [44].

## 9. Conclusions

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 enhance survival. While this three-pronged therapy has not been experimentally demonstrated intravenous thiamine combined with intravenous glucose yields superior survival compared to either intravenous glucose or intravenous thiamine administered singly [10].

Additionally, by illustrating that antibiotics have no impact on the course of the established sepsis process this may minimise excessive antibiotic usage.

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