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Review

Glucose homeostasis, nutrition and infections during critical illness

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ABSTRACT

Critical illness is a complex life-threatening disease characterized by profound endocrine and metabolic alterations and by a dysregulated immune response, together contributing to the susceptibility for nosocomial infections and sepsis. Hitherto, two metabolic strategies have been shown to reduce nosocomial infections in the critically ill, namely tight blood glucose control and early macronutrient restriction. Hyperglycaemia, as part of the endocrine–metabolic responses to stress, is present in virtually all critically ill patients and is associated with poor outcome. Maintaining normoglycaemia with intensive insulin therapy has been shown to reduce morbidity and mortality, by prevention of vital organ dysfunction and prevention of new severe infections. The favourable effects of this intervention were attributed to the avoidance of glucose toxicity and mitochondrial damage in cells of vital organs and in immune cells. Hyperglycaemia was shown to impair macrophage phagocytosis and oxidative burst capacity, which could be restored by targeting normoglycaemia. An anti-inflammatory effect of insulin may have contributed to prevention of collateral damage to host tissues. Not using parenteral nutrition during the first week in intensive care units, and so accepting a large macronutrient deficit, also resulted in fewer secondary infections, less weakness and accelerated recovery. This was at least partially explained by a suppressive effect of early parenteral nutrition on autophagic processes, which may have jeopardized crucial antimicrobial defences and cell damage removal. The beneficial impact of these two metabolic strategies has opened a new field of research that will allow us to improve the understanding of the determinants of nosocomial infections, sepsis and organ failure in the critically ill. **C. Ingels, CMI 2017;▪:1**

Introduction

Critical illness is a life-threatening condition with high mortality [1,2]. Thanks to major developments in critical care over several decades [1], most patients can now survive the initial insult that triggered admission to the intensive care unit (ICU). About 25% of patients, however, remain dependent on intensive care for more than a week, referred to as the prolonged phase of critical illness. This prolonged phase is characterized by profound endocrine and metabolic alterations driving a hyper-catabolic state and by a dysregulated immune response with ongoing low-grade inflammation and immunosuppression. As a result, protracted critical illness is associated with pronounced muscle weakness that further prolongs the dependency on vital support, and with an increased susceptibility to recurrent nosocomial infections and sepsis, together contributing to multiple organ dysfunction syndrome and ultimately even death [3,4].

Alteration of glucose homeostasis during critical illness

Hyperglycaemia, one of the consequences of the endocrine–metabolic responses to stress [5], is present in almost all critically ill patients upon admission to the ICU. Hyperglycaemia is induced by stress hormones such as cortisol, catecholamines, growth hormone and glucagon, and is aggravated by hyperglycaemic drugs such as vasopressors, parenteral nutrition and corticosteroids. It is brought about by macronutrient-resistant hepatic gluconeogenesis and glycogenolysis and by peripheral insulin resistance [6–8]. This hyperglycaemic response was originally described by Selye as a programmed, adaptive process, which was thought to provide a survival advantage [9]. However, pronounced

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and persistent hyperglycaemia is associated with poor outcome and was identified as an independent predictor of hospital mortality [10]. It remains a matter of debate whether hyperglycaemia is merely a marker of the magnitude of the stress response and so represents a surrogate for the severity of illness or is causally related to poor outcome [8,11].

Immune dysfunction during critical illness

The immune disturbances that occur during acute and prolonged critical illness defy simple characterization [12]. Depending on the stage of disease, the immune response has been reported as excessively activated or as hypo-responsive. Moreover, innate and adaptive immune processes might be influenced differently. Moving away from the old labels 'systemic inflammatory response syndrome' and 'compensatory anti-inflammatory response syndrome', for two syndromes that were believed to occur subsequently, new theories have now been proposed [13].

In the first theory, pro-inflammatory and anti-inflammatory responses are assumed to occur early and simultaneously after the initial insult. The net effect of these opposing processes is dominated by the early pro-inflammatory response. If the response is too intense, which could lead to exhaustion, or when the initial assault cannot be eliminated in a timely fashion, subsequent failure of elements of both the innate and adaptive immune system may lead to a chronic, immunosuppressed state or 'immuno-paralysis' [13–15]. The second theory, based on gene expression data from circulating leucocytes, states that the early activation of the innate immune system persists beyond the immuno-paralysis phase, causing persistent low-grade inflammation [16], which in turn leads to late mortality, due to intractable inflammation-induced organ damage [4].

The driving forces behind these immune changes remain poorly understood. Exhaustion of immune cells, accelerated apoptosis or leucocyte reprogramming have been suggested as possible contributing mechanisms [13,17,18]. Recently, it was proposed that an acquired immune dysfunction, leading to an impaired defence of the host against infection, might in part be caused by failure of immune cells to adapt glucose metabolism. Indeed, intact immune cells are able to increase the conversion of glucose to lactate, even in the presence of normal oxygen levels, to boost their energy production to mount a potent inflammatory reaction. This metabolic adaptation, which is also seen in tumour cells (Warburg effect), appears to fail in circulating white blood cells at the onset of secondary infections possibly as a consequence of epigenetic reprogramming that occurs during critical illness [19,20].

Increased susceptibility to nosocomial infections and sepsis

Due to the various derangements in—or resetting of—homeostatic mechanisms, critically ill patients are at great risk of contracting nosocomial infections, which not only cause accrued morbidity and mortality, but also generate extra costs to the health system [21]. Ventilator-associated pneumonia is the most common infection in selected groups of critically ill patients (68%), followed by abdominal infections (22%), bloodstream infections (20%) and urinary tract infections (14%), and carries a risk of death [22–24].

From an evolutionary point of view, short-term and moderate hyperglycaemia might be beneficial during the acute stress of trauma or illness to ensure supply of glucose to immune cells when the host is unable to feed normally [25]. There is some evidence that brief hyperglycaemia could activate anti-apoptotic pathways and favour angiogenesis [26,27] and could fuel the production of NADPH [28], which is needed for the formation of reactive oxygen species by macrophages [8]. However, there is equally compelling evidence for a harmful effect of severe and/or persistent hyperglycaemia on immune function [29]. Indeed, stress-induced hyperglycaemia may contribute to infections as high glucose levels negatively affect all major components of the innate immune response [29], and can induce aberrant glycosylation of proteins, enzymes and immunoglobulins that can alter the adaptive immunity [30,31]. As an example, high glucose levels are known to inhibit neutrophil migration and function, decrease phagocytosis capacity, and impair complement fixation and immunoglobulin-mediated opsonization of bacteria [32,33]. These mechanisms explain the observed association between hyperglycaemia in patients with diabetes mellitus who undergo cardiac surgery and their increased risk of acquiring nosocomial infections [34].

On the other hand, critical illness *per se* can profoundly alter immune pathways, adding to the high risk of secondary nosocomial infections. These secondary infections are often caused by opportunistic pathogens and fungi or result from reactivation of dormant viruses (e.g. cytomegalovirus) [13–15]. Sepsis is the clinical syndrome characterized by life-threatening organ dysfunction that is caused by a dysregulated host response to infection [35]. It is considered to be the prototypical consequence of a maladjusted immune response. Sepsis has a high acute mortality due to overwhelming inflammation, but immunosuppression presenting after the initial pro-inflammatory peak is considered to be responsible for a substantial late morbidity and mortality [13]. Recent research demonstrates that sepsis directly, or indirectly, impairs the function of virtually all immune cells. Sepsis is associated with accelerated apoptosis of most immune cells, decreased cytotoxic and antigen-presenting capacity, diminished production of pro-inflammatory cytokines, and reduced antibody production [13]. Hence, sepsis-induced dysfunction in innate and adaptive immune components contributes to a blunted immune response to microbial challenge and to the risk of secondary infections [19].

Reducing infections in the critically ill via metabolic strategies

Traditionally, preventive strategies to reduce infections have focused on reducing the exposure to bacteria as bacterial colonization is thought to precede the establishment of infection. These strategies comprise surveillance, disinfection and hand hygiene and selective decontamination, among others [36]. More recently, concern was raised that bacterial colonization may in fact already be the first symptom rather than the cause of nosocomial infections [36]. If this is the case, in order to reduce infections, preventive measures should be directed towards the causes of the impaired immune defence. Hitherto, two metabolic strategies have shown this potential: tight blood glucose control and early macronutrient restriction.

The potential of tight blood glucose control

As mentioned above, hyperglycaemia, as part of the stress response, is common during critical illness and is associated with an increased risk of morbidity and mortality [37,38]. To test the hypothesis that such a response, when pronounced and sustained during critical illness, causally contributes to morbidity and mortality, a first proof-of-concept randomized controlled trial (RCT) of 1548 patients was conducted in a surgical ICU in Belgium [39]. The aim of this study was to compare the contemporary 'usual care', tolerating hyperglycaemia, with 'intensive insulin therapy', targeting normoglycaemia. Indeed, at that time, usual care consisted of tolerating pronounced hyperglycaemia as an adaptive mechanism and only to start insulin when blood glucose levels exceeded the renal threshold (12 mmol/L or 215 mg/dL) above which glucosuria appears and potentially induces hypovolaemia. On the

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