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REVIEW

Acute Inflammation and Metabolism

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Abstract— Inflammation is an adaptive process to the noxious stimuli that the human body is constantly exposed to. From the local inflammatory response to a full-blown systemic inflammation, a wide complex sequence of events occurs. Persistent immunosuppression and catabolism may ensue, until multiple organ failure finally sets in. And since clinically useful and specific biomarkers are lacking, diagnosis may come late. A thorough understanding of these events (how they begin, how they evolve, and how to modulate them) is imperative, but as yet poorly studied. This review aims to consolidate current knowledge of these events so that the management of these patients is not only evidence-based, but also built on an understanding of the inner workings of the human body in health and in disease.

KEY WORDS: inflammation; metabolic stress; systemic inflammatory response syndrome; multiple organ dysfunction syndrome; CARS; PICS.

The human body is exposed constantly to external noxious stimuli. Throughout its evolutionary process, it has developed multiple mechanisms to detect, respond to, and repair with the aim of maintaining homeostasis. Inflammation is the adaptive response to those stimuli, whether it is imparted by infection, trauma, surgery, burns, ischemia, or necrotic tissue. It is not an all-or-nothing process; hence, the term "para-inflammation" is used to describe the cellular state between tissue homeostasis and a full-blown inflammatory response [1, 2].

Inflammation exerts important effects on metabolic and neuroendocrine functions, much of which are yet to the fully elucidated. Consequently, there are many potential implications waiting to be clinically validated [1].

This review is divided into three sections: "THE FUNDAMENTAL PRINCIPLES" describes the fundamental principles of inflammation and metabolism; "ENHANCED FUNDAMENTAL PRINCIPLE" looks into more advanced clinical concepts; "PRACTICAL IMPLICATIONS FOR CLINICIANS" outlines how this knowledge can be applied to clinical practice.

THE FUNDAMENTAL PRINCIPLES

There is more to inflammation than the four classic signs of redness, swelling, heat, and pain. Rudolph Virchow added in 1858 a fifth sign—disturbance of function—and it would prove to be a key player in the events that accompany inflammation, both locally and systemically [2].

The Inflammatory Pathway

The inflammatory process has been best studied in response to infectious stimuli, particularly bacterial infections. It is not clear whether most of the principles studied in infection-induced inflammation apply to other causes.

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However, a generic inflammatory pathway has been proposed.

This pathway consists of inducers, sensors, mediators, and effectors. The inducers can be either infectious organisms or non-infectious stimuli, such as toxins, foreign bodies, signals from necrotic cells, and damaged tissues. Sensors are specialized molecules that are activated by the inducers, which trigger the production of mediators. The mediators are endogenous chemicals that can induce the feeling of pain, can either promote or inhibit inflammation and tissue repair, and can activate the effectors—tissues and cells [1]. The conjugation of these multiple players gives rise to many alternative routes in the inflammatory pathway and which path is taken depends on the inciting stimuli. For a sterile stimulus, one of the goals is to prevent infection on the injured tissue. However, this cannot always be done successfully [2].

Inducers can be classified as pathogen-associated molecular patterns (PAMPs), which are molecular patterns from infectious organisms, and as damage-associated molecular patterns (DAMPs), molecules released from damaged cells of the host. Each of these patterns is recognized by different receptors in macrophages and dendritic cells; pain receptors also sense tissue damage. Inflammatory cytokines are released after stimulation of those receptors [2, 3]. They include TNF-α, IL-1, IL-6, among others, which induce changes on the endothelium, allowing the passage of immune cells through the junctions between endothelial cells.

The immune cells that are recruited depend on the inflammatory state of the tissue: para-inflammation leads to recruitment of monocytes, while a full-blown inflammation also leads to the translocation of neutrophils to the tissue [2]. These cells will then release enzymes that fight off infectious organisms and clear dead cells.

As a consequence of this enzyme release, reactive oxygen species (ROS) will accumulate in tissues. These are known to damage healthy cells [1]. Endothelial cells also release pro-inflammatory cytokines which further attract inflammatory cells. Plasma also translocates to adjacent tissues, leading to tissue edema. Circulating platelets are also activated and aggregate, while anticoagulant protein synthesis is reduced. This can lead to intravascular thrombosis, which, in excess, could contribute to organ dysfunction [4, 5]. Figure 1 summarizes the events that lead to the five cardinal signs of inflammation.

The sum of these events may have to do some harm to do good. Indeed, disturbance of function is the only sign of inflammation that accompanies all the inflammatory events, regardless of their origin [2]. For example, tissue edema that forms due to local inflammation can increase hypoxia in the tissues, which by itself promotes inflammation [6]; tissue hypoxia is clinically important and, as described in the third section, truly useful point-of-care biomarkers of tissue hypoxia are lacking [7].

The Role of Immune Cells in Regulating the Inflammatory Response

In a full-blown inflammation, neutrophils are the first immune cells to arrive and translocate to tissues. Neutrophils synthetize ROS, stimulated by external factors such as PAMPs and DAMPs, in order to clear external harmful substances and also those that are engulfed. Consequently, ROS are present both intracellularly and extracellularly. Intracellular ROS enables the formation of an active inflammasome, a group of proteins which will trigger further inflammation through the cleaving of precursors of pro-inflammatory proteins. Neutrophils also release chemoattractant proteins that promote migration of monocytes to tissues. Here, monocytes differentiate into macrophages, either M1 or M2. M1 macrophages further produce ROS and recruit other immune cells, while M2 act at a later phase, as they promote tissue repair by releasing growth factors [8, 9]. TNF-α is one of the most important inflammatory cytokines released by M1 macrophages, as it induces systemic effects, as latter described [1, 10, 11]. The phenotype of macrophages is strongly linked to metabolism, as M1 cells are mainly glycolytic, while M2 oxidize fatty acids [9].

The accumulation of metabolites, such as lactate, and the local concentration of nutrients is believed to influence the timing of M2 differentiation [9]. Effective clearance, by macrophages, of neutrophils that have suffered programmed cell death is also important to subside the inflammatory stimulus [12]. The timing for resolution of inflammation is critical, as there is risk that the inflammatory process remains active, hence chronic, and ROS and oxidative damage then prevails [9].

Accumulated ROS also play an important role in setting the moment where inflammation resolves [9], as they also serve as important signaling molecules, regulating cell growth, differentiation and apoptosis [8]. However, ROS in high concentrations are harmful to tissues, both local and distant. Hydroperoxides, in particular, may spill from the inflamed tissue and reach the circulation, where they may damage blood cells, plasma proteins, and even reach distant tissues by means of small vesicles called exosomes [13].

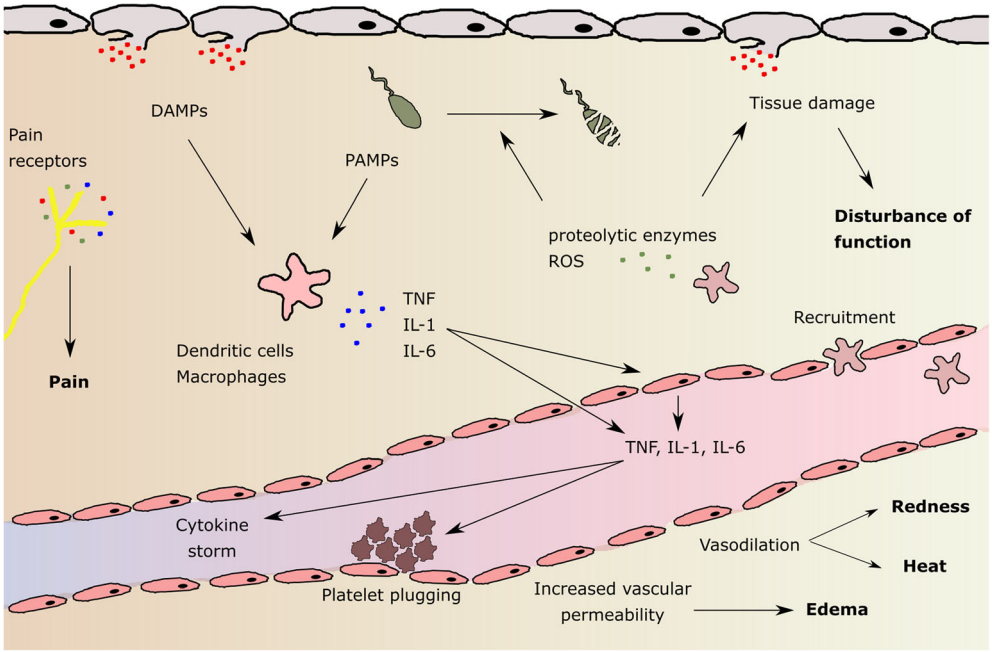

Fig. 1. Tissue and vascular changes during a local inflammatory event; the five cardinal signs of inflammation are in bold (for references, see text); DAMPs damage-associated molecular patterns; PAMPs pathogen-associated molecular patterns; ROS reactive oxygen species.

The Acute-Phase Response

Released pro-inflammatory cytokines create a pro-inflammatory loop that can break away from the injured tissue and enter the bloodstream, leading to what has been called the "cytokine storm". TNF-α is one of the many cytokines involved in this process [5, 14]. Organ-specific receptors are activated by these cytokines and a systemic reaction ensues. This systemic reaction is called the acute-phase response, and here, the liver is the major player. The liver begins increasing the production of certain proteins—C-reactive protein, serum amyloid A, haptoglobin, fibrinogen, α-globulins with antiprotease-activity, lipopolysaccharide binding protein, ceruloplasmin, complement factor-3—and decreasing the synthesis of others, which leads to the decrease in certain substances in serum—zinc, iron, albumin, transferrin, cortisol-binding globulin, transthyretin, and retinol-binding protein. The purpose of each of these changes in protein quantity has not yet been fully clarified, but scavenging pathogens and modulation of the inflammatory response and its consequences may be an important goal [15, 16].

C-reactive protein is the best clinical indicator of the acute-phase response [17], although it does not distinguish between the different causes of inflammation [18], while albumin has the disadvantage of also being decreased in case of malnutrition [19] and elevated in dehydration [20].

Another site where the circulating cytokines act is in the brain endothelium, leading to the release of prostaglandins, which are responsible for the symptoms of lethargy, anorexia, and fever, a positive adaptive response to infection [2, 17].

Further changes occur during inflammation, namely an elevated metabolic rate, with muscle catabolism to retrieve amino acids, essential for tissue repair and synthesis of proteins for the immune response to the lesion; the outcome of this is muscle wasting [17].

The Interplay Between Inflammation and the Neuroendocrine Response

Any response to a stressor involves a neuroendocrine as well as the inflammatory response already detailed. This neuroendocrine response involves the sympathetic nervous system (through release of norepinephrine from post-ganglionic neurons and of epinephrine by the adrenal medulla) and the hypothalamic-pituitary axis (release of adrenocorticotropic hormone, thyroid-stimulating hormone, growth hormone, follicle-stimulating hormone, and luteinizing hormone). This response is initiated when afferent nerves, baroreceptors, and chemoreceptors are

activated by the stressor and its effects [21]. For instance, trauma to a limb may cause lesion to the tissues leading to local inflammation (cytokines will spill over the affected site), may cause activation of afferent nerves (sending that signal to the brain), and may even cause hypovolemia from blood loss (activating baroreceptors). TNF-α also exerts a great effect in activating the hypothalamic-pituitary axis [11].

Cytokines will quickly induce a state of growth hormone resistance in peripheral tissues, leading to an increase in its serum levels early in illness. Growth hormone promotes anabolism, so the net effect is now a catabolic response, with mobilization of glucose and fatty acids [22].

Regarding thyroid hormones, serum T3 levels decline, while reverse T3 levels increase. TSH usually remains in the low to normal concentrations. This is called euthyroid sick syndrome [23]. The decrease in T3 levels in the first 24 h is associated with the magnitude of the illness and lower T3 levels are associated with higher mortality. There is no solid explanation for this decrease, but it could serve to reduce catabolism [22].

Serum levels of testosterone are also decreased, and this also seems to decrease anabolism that this hormone usually stimulates. Prolactin levels increase in a stress response; this change is not well explained, but it is understood to be a key player in activating the immune system [22].

Cortisol increases in acute illness, probably related to the severity of the stressor. Nevertheless, low levels may also be present, and they reflect an insufficient response to stress, termed "relative adrenal insufficiency". The cortisol surge leads to mobilization of protein and glucose storages [22].

Modulating this response with exogenous hormones has been studied with disappointing results [22]. This will be further reviewed in the third section of this article.

Metabolic Stress, Catabolism and Reactive Oxygen Species Escalation

The neuroendocrine response together with the inflammatory response leads to mobilization of energy storages, triggering the release of fatty acids by lipolysis, the release and degradation of glucose from glycolysis, glycogenolysis, and gluconeogenesis in the liver and release of amino acids from muscle proteolysis; amino acids may be used in the liver to form new glucose. TNF-α, as described before, has been implicated in this catabolic state, particularly in glycolysis and lipolysis [10]. Lactate is one of the bridge-molecules between the liver and the muscle in energy source mobilization [21, 24]. The heart, which uses mainly fatty acids for energy, switches to lactate as its primary fuel in shock states [7].

Muscle wasting is one of the main consequences of this deployment of storages and is worsened by the excess cortisol that impairs protein synthesis [17]. This creates a negative nitrogen balance, which is the difference between nitrogen intake and loss; its calculation is based on urinary urea nitrogen excretion plus 4 g/day (corresponding to loss in other locations). Few studies to date have evaluated its usefulness [25]. In order to overcome the synthesis block by cortisol and the catabolism, an increase in protein supplementation during this time has been proposed, but there is insufficient evidence for its effectiveness [26, 27].

All this culminates in uncontrolled catabolism and resistance to anabolic substances, such as insulin, giving rise to hyperglycemia [21]. These catabolic events may parallel those of the "flow" phase of post-traumatic metabolic response (which follows the brief "ebb" phase of decrease in temperature and oxygen consumption), where it has been associated with severe complications stemming from hyperglycemia, hypoproteinemia, and immunosuppression [28].

ROS are further formed from this intense catabolism, promoting inflammation, which further leads to release of more ROS [21]. The effects of hydroperoxides have already been mentioned, while their parent compound, hydrogen peroxide (H_2O_2), has also been implicated in the pathogenesis of septic shock, by fostering coagulopathy, capillary leakage, and immunosuppression [29]. Excess ROS consumes glutathione, an antioxidant dependent on glutamine for its synthesis, again leading to more ROS because of depletion of this antioxidant. When corrected, hypoperfusion of tissues that may accompany the initial injury, mostly from obstruction by microthrombi and leukocyte and platelet plugs [30], will cause the release of cytokines and of ROS by those tissues, an event termed ischemia-reperfusion injury. System-wide inflammation may ensue [31]. Hypoperfusion leads to inadequate supply of oxygen to tissues, a condition named "tissue hypoxia"; hypovolemia and cardiogenic shock both cause organ injury through this mechanism. Cytopathic hypoxia, on the other hand, refers to the inability of the mitochondria to use oxygen caused by the inhibition of enzymes that make the metabolic transition from cytoplasm to energy production in mitochondria. This inhibition may be due to toxins released by infectious organisms and is thought as being the cause of tissue injury in sepsis and septic shock [32]. Biomarkers that would allow for distinction between these two mechanisms are needed.

ROS may then cause the premature death of mature red blood cells, called eryptosis. Erythropoietin (EPO) inhibits eryptosis, but inflammation results in decreased EPO production. Young red blood cells are also destroyed, in neocytolysis, triggered by a fall in EPO levels. Anemia may ensue [33].

Recently, autophagy has been regarded as beneficial in metabolic stress. It involves the degradation of intracellular contents and is the only process that can remove macromolecular damage, such as those related to ROS. It is activated by starvation, exercise, and several stress signals and it is inhibited by insulin therapy and artificial feeding (amino acids being the macronutrients with more effect on it). Protection against organ failure conferred by autophagy was noted in critically ill animal models and it seems particularly important in preventing acute kidney injury after ischemia-reperfusion injury [34, 35].

Euglycemia seems to increase protein synthesis, namely glutamine, the major component of glutathione, as well as decrease protein catabolism [21], which could be helpful in attenuating the effects of ROS and cortisol.

The peri-surgical acute period is an example of intense catabolism where multiple causes may contribute to the hypermetabolic response, from the acute stress event that leads to surgery, the surgery itself, to the post-operative recovery. Some factors affecting the response of the individual to these are age, nutrition, anesthesia, and invasiveness of the surgery. First, as individuals get older, their hormonal response to stress events lasts longer, so a second or third hit may occur when the patient still has not recovered from the previous hits. Protein degradation, one of the hallmarks of the metabolic stress, seems to be reduced by refraining from using general anesthetics. There is also evidence of lesser levels of inflammatory markers by choosing laparoscopic to open surgery [36]. Pain management also contributes to lessen the inflammatory burden associated with neuroendocrine activation [37]. Figure 2 shows the metabolic changes during a stress event.

ENHANCED FUNDAMENTAL PRINCIPLES

Having reviewed the basic principles of inflammation and how it affects the metabolism of individuals in the previous section, this section makes the transition from the bench to the bedside, where seriously ill patients with organ failure reflect the culmination of the constant interplay between the multiple cellular and tissue processes that have been detailed previously.

The Systemic Inflammatory Response Syndrome

If the initial stimulus for the inflammatory response is not cleared successfully by the inflammatory process or if it lingers on, chronic inflammation may ensue or it may progress to a system-wide process, beyond the organ initially afflicted, inducing a systemic inflammatory response syndrome (SIRS) [2, 38]. Clinically, SIRS is based on the presence of two out of four criteria: fever (> 38.0 °C) or hypothermia (< 36.0 °C), tachycardia (> 90 beats/min), tachypnea (> 20 breaths/min), leukocytosis ($> 12 \times 10^9$/L), or leucopenia ($< 4 \times 10^9$/L) [39].

What is known about this transition from local inflammation to SIRS depends on each inciting stimulus of inflammation. The best studied cases are pancreatitis and infections progressing to sepsis (SIRS plus suspected or confirmed infection) [40, 41]. SIRS by itself is associated with increased mortality in patients admitted to the emergency department and this has been found to be a predictor of infection, severity of disease and organ failure [42]. However, when comparing the discriminative power for mortality in patients presenting to the emergency department, SIRS plus suspected or confirmed infection is less useful than the more recent Sepsis-3 criteria [43]. The progression of SIRS leads to multiple organ dysfunction syndrome (MODS) [41].

Multiple Organ Dysfunction Syndrome

The transition from SIRS to MODS is also not clearly elucidated. MODS is defined as the failure of two or more organ systems in the acutely ill patient. This may originate from the increased vascular permeability induced by circulating cytokines, leading to inflammatory mediators leaking to different tissues, and initiating a new local inflammatory process, with increasing impairment of tissue functions. Again, ischemia-reperfusion injury and ROS may also contribute [31, 38]. Microvascular thrombosis, caused by endothelial and platelet activation by cytokines, and leading to disseminated intravascular coagulation, has also been proposed [4]. Tissue hypoxia is also a key factor, as the higher the oxygen debt (the cumulative deficit of tissue oxygenation) the greater the risk of multiorgan failure [32].

According to the European Society of Intensive Care Medicine guidelines, organ dysfunction is regarded as a continuum of physiologic derangement (of decreasing organ dysfunction), while organ failure is defined as a dichotomous event that is either present or absent [44].

In the intensive care unit (ICU), organ dysfunction is scored according to the sequential organ failure assessment (SOFA) score and Marshall Multiple Organ Dysfunction

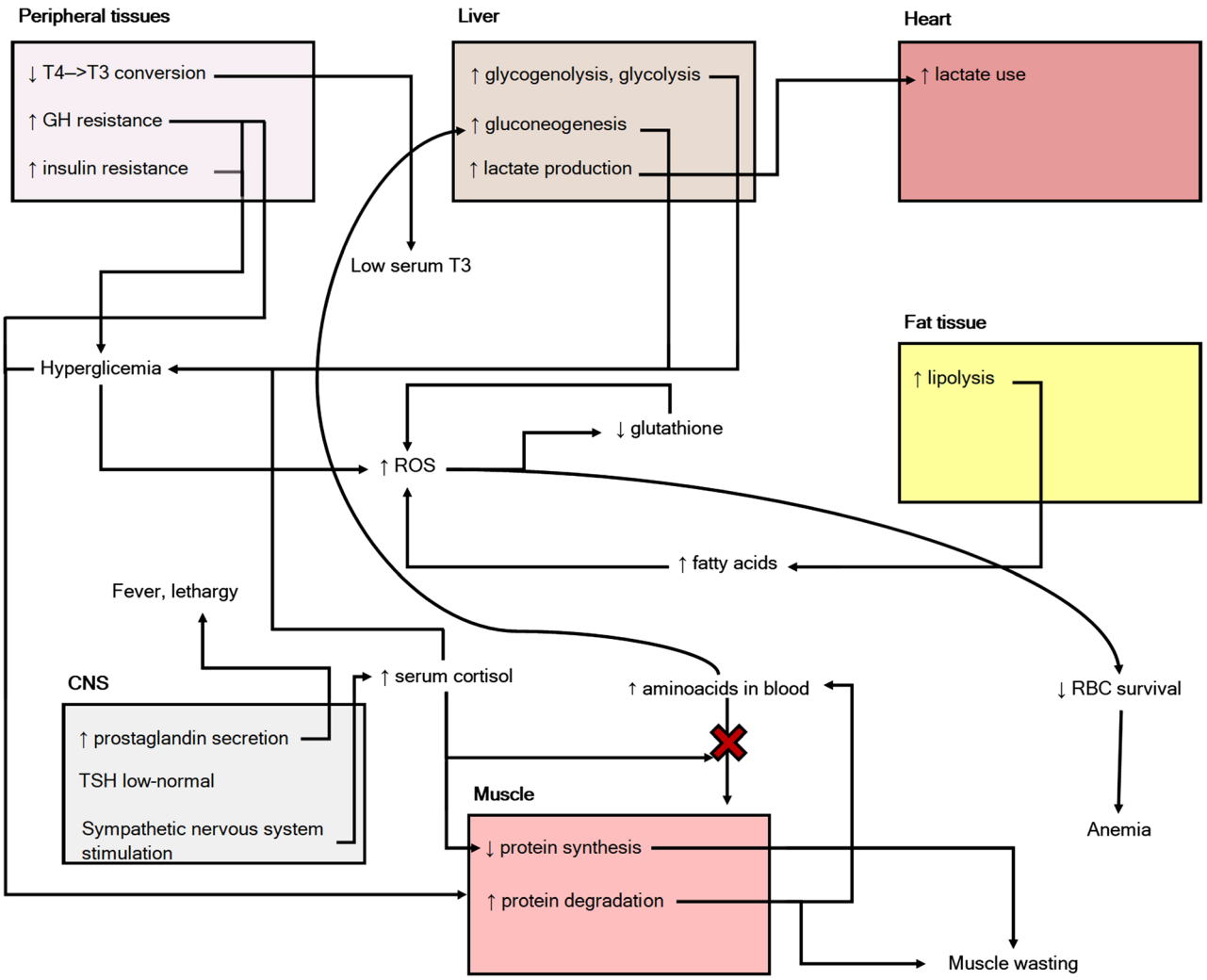

Fig. 2. Metabolic changes during a stress event (for references, see text); CNS central nervous system; GH growth hormone; RBC red blood cell; ROS reactive oxygen species.

Score (MMODS), among others. They score for dysfunction in respiratory, cardiovascular, hepatic, hematologic, neurologic, and renal systems. As the score increases, so does the mortality. Both the SOFA score and MMODS are very sensitive but not specific for organ failure. Ayman El-Menyar et al. present in their paper an interesting list comparing the multiple organ dysfunction scoring systems [31, 45].

The respiratory system usually is the first system to fail in MODS; here, the capillary leakage leads to cells and inflammatory proteins moving to the interstitial space and consequently flooding of alveoli. Surfactant production by type II alveolar cells is decreased, eventually leading to alveoli collapse. This increases pulmonary shunt. Acute respiratory distress syndrome may soon follow [38].

Vasodilation due to cytokines leads to hypotension, with a decrease of systemic vascular resistance, and, together with the shift of fluid to the interstitial space, less blood is returned to the heart, potentiating tachycardia and temporarily inducing an increase in myocardial contractility to increase systolic volume. Myocardial depression then ensues and an increase in central venous pressure follows the failing heart [38]. Peak early diastolic transmitral/peak early diastolic annular velocity (E/e′), as measured by echocardiography to determine diastolic dysfunction, has better prognostic prediction of hospital mortality in septic

shock than cardiac biomarkers (troponin T, BNP, NT-proBNP) [46].

Central nervous system dysfunction is usually a neglected early event. It may present itself as confusion, agitation, lethargy, or coma. It is also one of the most long-lasting dysfunctions in MODS [45].

Hepatic system dysfunction includes transaminase elevation from "shock liver", coagulation abnormalities, and hyperbilirubinemia. Hypoperfusion results in "shock liver", also leading to the former two abnormalities. Acute liver failure may ensue [45]. Liver dysfunction may begin before there is clinical evidence of it [38]. Of note, there is conflict in the literature regarding the definition of liver failure, with some authors relying in bilirubin and mental changes, while others also mentioning liver enzymes or changes in the International Normalized Ratio [47, 48]. The AASLD 2011 position paper on liver failure defined it as INR ≥ 1.5 and any evidence of altered sensorium in patients with clinical or laboratory evidence of acute hepatitis [49]. Both the SOFA score and the MMODS rely on bilirubin to score liver function [45], although in pure hyperbilirubinemia, the hepatic synthetic function is not affected [45].

Gastrointestinal motility is usually decreased, leading to ileus and abdominal distension. It is also prone to ischemia due to blood shunting to perfuse other noble organs. As the intestinal lumen harbors numerous populations of bacteria, the breakdown of the intestinal barrier following mucosal ischemia will result in bacteria translocation, further increasing systemic inflammation [38].

A decrease in perfusion and the inflammatory mediators is also the reported causes for acute kidney injury (AKI) in MODS [38]. In septic states, however, renal blood flow is preserved and the main perfusion issues occur at the microvascular level, as inflammatory cytokines cause increased expression of adhesion molecules and increased leukocyte trafficking, which contributes to capillary stasis [50, 51]. AKI is the component of MODS that most predicts mortality. Renal replacement therapy is indicated for intractable fluid overload, hyperkaliemia (potassium concentration > 6.5 mmol/L or > 5.5 mmol/L with electrocardiogram changes), severe metabolic acidosis (pH < 7.1), uremic encephalopathy, and pericarditis [52]. AKI in sepsis could be predicted by measuring urinary cystatin C [46].

Thrombocytopenia, with multifactorial etiology, and anemia, due to bone marrow suppression, are the most common hematologic repercussions in MODS [45].

Each organ dysfunction, however, may not be a contained event, as more evidence has been emerging related to the concept of organ cross-talk. Organ cross-talk is a complex communication between various organs, through mechanical and molecular signals, which maintain homeostasis. Yet, it can also have deleterious effects when one organ fails, as that organ may induce changes remotely on other organs, whether acutely or chronically [53]. ROS, as mentioned previously, may be part of some of these molecular signals. The most studied reciprocal pathological interactions are between the heart and lung, heart and kidney, kidney and lung, and kidney and liver [53–55]. There is some evidence that the intestine could also be affected when injury to the liver occurs and afterwards induce failure of other organs [56].

As mentioned previously, there is increased catabolism, with total energy expenditure often increased 1.5–2 times the normal. Muscle wasting occurs early in the first week of critical illness and is more severe in those with multiple rather than single organ failure. Survivors may experience muscle weakness and physical disability for at least 5 years after the critical illness [57]. Nutritional support plays an important part in managing the patient with MODS. Pre-albumin and transferrin, due to their shorter half-lives than albumin, have been advocated as markers to determine response to nutritional support, yet current recommendations argue against it [38, 58, 59].

Challenging the Concept of SIRS-MODS Sequence

Unlike previously thought, SIRS is not a single all-out unregulated response, as a compensatory anti-inflammatory response (CARS) occurs with SIRS. CARS is regarded as a delayed response to SIRS, but some authors argue that it occurs at the same time SIRS begins [60]. Just as SIRS is associated with multiple organ failure (MOF), so does CARS can, in excess, lead to greater complications, such as immunosuppression. CARS is clinically expressed as hypothermia, leukopenia, and failure to clear infection [52, 61]. SIRS may superimpose and lead to early MODS, where TNF-α and IL-1 take center stage, leading to early mortality. Alternatively, through IL-10 and IL-6, CARS could predominate and result in immunosuppression and, ultimately, sepsis, with late MODS and late mortality. Indeed, in early survivors of acute pancreatitis, a higher rate of infections is seen later in the course of the disease [41]. Early MODS, with less incidence, occurs within 3 days, and is associated with high mortality, while late MODS, accounting for 60% of cases of MODS, occurs after 3–7 days and causes less mortality. Early MODS is associated with respiratory and later cardiac dysfunction, while in late MODS, liver and kidney dysfunction predominate [31, 52].

With advances in medical care, especially in intensive care, late MODS has decreased and a new entity has surfaced: persistent inflammation-immunosuppression catabolism syndrome (PICS). PICS is proposed as a diagnosis for patients who have a prolonged stay in the ICU with manageable organ dysfunctions, with protein catabolism, poor nutritional status, poor wound healing, immunosuppression, and recurrent infections. They also typically develop decubitus ulcers and tend to suffer from increased levels of pain, dyspnea, fatigue, and delirium [60]. It is a vicious cycle, as the patient is persistently in a state of systemic inflammation, while on a poor immune status. In a persistent inflammatory-catabolic state, patients have few resources to induce the anabolic response that would allow the person to recover and fight new infections, thus leading to recurrent infections which in turn promote ongoing inflammation [52]. Table 1 shows the diagnostic criteria for PICS and Fig. 3 shows the relation between SIRS, CARS, MODS, and PICS.

Despite the intense catabolism of patients in PICS, there is no evidence on how to provide them with nutritional support [60]. PICS is regarded as the next challenge in surgical critical care [62], yet clinicians that treat older people in internal medicine infirmaries may find that a sizable proportion of their patient may also fit this syndrome, even if the definition of PICS only includes ICU patients. In the elderly, particularly, this syndrome could be closely linked to the emerging concept of frailty, a state of vulnerability with limited physiologic reserve to cope with stressors, such as trauma or infection. At least three out of the following criteria must be fulfilled to diagnose frailty: weight loss, fatigue, low physical activity, slowness, and weakness [63].

PRACTICAL IMPLICATIONS FOR CLINICIANS

Being a very complex subject with multiple interactions in many metabolic pathways and a great clinical heterogeneity, much is unknown about the diagnosis, prevention, and treatment of inflammation-associated organ dysfunction. This section builds upon the information already presented to describe clinical recommendations for biomarker use and management of patients with inflammation-induced metabolic changes.

Table 1. Diagnostic Criteria of PICS (adapted from [52])

• ICU stay ≥ 10 days
- Persistent inflammation
- C-reactive protein concentration > 150 μg/dl
- Retinol binding protein concentrations < 10 μg/dl
• Immunosuppression
- Total lymphocyte count < 800/mm3
• Catabolic state
- Serum albumin concentrations < 3.0 g/dl
- Creatinine height index < 80%
- Weight loss > 10% or BMI < 18 during the current hospitalization

Assessing the Metabolic Implications of Inflammation—the Role of Biomarkers

Most biomarkers are still no used in clinical practice, despite promising results, whether it is due to prohibitive cost, poor availability, or ease of use. Currently, there are three biomarkers of interest which are already being used in the care of the acutely ill patient in which an inflammatory process is thought to be taking place that will be detailed here: C-reactive protein, procalcitonin, and lactate. Soluble triggering receptor expressed on myeloid cells (sTREM-1) is a promising new marker. Albumin will also be briefly referred.

C-reactive protein, as stated before, is an acute-phase response protein, whose levels increase 2 h after the acute insult, reaching its peak at 48 h [31]. It may take several days to decline. It has low specificity, since it can be elevated in infections, inflammatory disease, myocardial infarction, acute pancreatitis, after surgery, burns, trauma, lymphoma, or carcinomas [64]. As its levels may rise in response to trauma or surgery, it is difficult to distinguish between these causes and an ensuing infection developing from one of these events. Thus, when C-reactive protein is elevated, difficulty exists in distinguishing between surgery or trauma and infection developing secondarily [18].

Procalcitonin, the prohormone of calcitonin, is released in response to activation and adherence of monocytic cells, mainly due to bacterial infection. It can be detected in blood samples at 6–12 h after the infectious stimuli, reaching its peak values between 12 and 48 h. Values higher than 0.5 ng/mL should prompt a diagnosis of infection and the initiation of antibiotics. It can also be used to support the decision to terminate antibiotic treatment, when levels have decreased by more than 90%, without impacting mortality [18, 65]. Procalcitonin can also be induced by severe trauma or prolonged cardiogenic shock, which also makes the use of this biomarker difficult in distinguishing between the different causes of SIRS.

sTREM-1, which has already been used clinically, is more specific for inflammation secondary to infection than C-reactive protein or procalcitonin. Its ability to distinguish between SIRS and sepsis has been evaluated in multiple studies, with poor results. However, its levels seem to

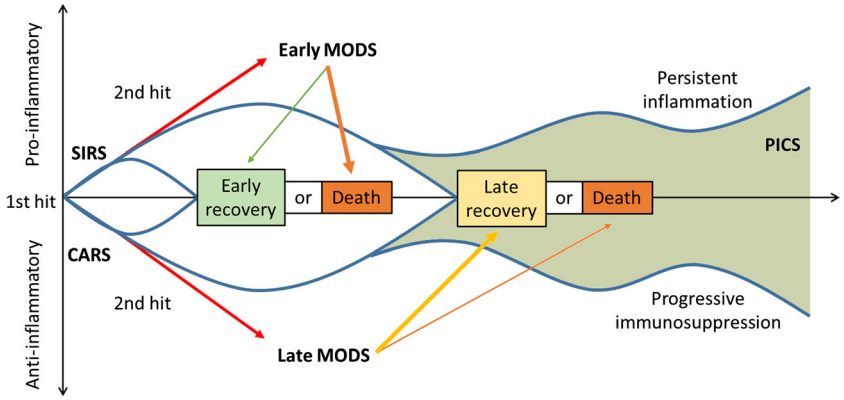

Fig. 3. SIRS-CARS, MODS, and PICS model (adapted from [52, 62]).

correlate with severity of the inflammatory process in pancreatitis, risk of developing remote organ failure, and the presence of infected necrosis [65, 66].

Lactate, when increased, is regarded as a marker of inadequate oxygen delivery and anaerobic metabolism. However, it can also be due to increased aerobic glycolysis as consequence of excess beta-adrenergic stimulation, an evolutionary survival response in the setting of increased metabolic stress [7, 67]. Marik and Bellomo argue that accelerated lactate clearance could compromise cardiac function, because, as already stated in this text, the heart switches to lactate as the main fuel during shock [7]. Lactate is also part of the liver-muscle exchange of substrates to mobilize energy sources. This could have implications in future treatment of these patients.

Nevertheless, research has shown that there is an association between lactate levels and organ failure and mortality, both in sepsis and trauma patients [68], and resuscitation guided by reduction of those lactate levels does reduce mortality [67]. In septic patents, an initial lactate level equal or higher than 4 mmol/L was associated with higher mortality [32]. In post-operative patients, however, lactate levels upon diagnosis of SIRS did not have an association with organ failure, but increased levels during the first 24 h after the diagnosis were associated with increased mortality [69]. Studies should address the cellular implications of manipulating this excess lactate, especially how they adapt their fuel sources as lactate is cleared and how exactly lactate decreases with current treatments: is there a decrease in metabolic stress with decrease in production or does organ function improve and therefore allows lactate to be converted to other substrates?

Albumin is of little use as it is not specific, as stated before. Still, its levels at ICU admittance inversely correlate with mortality [70]. When used in conjunction with urea, as serum urea to albumin ratio (UAR), an increased UAR predicted increased mortality in non-chronic kidney disease patients [71].

Modulating the Metabolic Response to Inflammation

As of today, no evidence supports giving growth hormone to critical patients [22, 23]. Corticosteroids, namely hydrocortisone, is currently not recommended for septic patients, unless fluids and vasopressors are not able to manage hemodynamic instability [67]. This recommendation, however, does not take into account whether the patient has adrenal insufficiency, for which there are no expert recommendations [72].

Euthyroid sick syndrome (ESS) has been previously mentioned and clinically comprises four stages: depressed serum T3 levels 24 h after the onset of the illness, elevation of T4 levels early in the acute illness, return of T4 levels to normal or subnormal range, and the normalization of thyroid hormone serum concentrations. The last stage may take weeks to months to occur after the acute illness has resolved. In ESS, TSH serum levels are low-normal to normal, but can be lower. Clinicians should be aware of these changes as to avoid erroneously diagnosing thyroid abnormalities as the changes are solely due to acute illness, especially since patients with ESS may experience signs and symptoms of hypothyroidism [23]. Thyroid hormone supplementation has not been shown to consistently improve outcomes. Low T3 serum levels were associated with increased mortality in patients with heart failure or liver cirrhosis and with worse prognosis in burn patients and end-stage kidney disease. Early nutrition in postoperative patients has been shown to prevent ESS [73].

The only firm evidence of good outcomes in manipulating the endocrine response is in maintaining euglycemia (between 140 to 180 mg/dl), as it has been shown to decrease mortality and morbidity in critically ill patients [21, 74, 75].

Modulation of the "cytokine storm" could prove useful in the future, not only in preventing the endocrine changes from cytokines but also the progression from local inflammation to SIRS.

Nutrition

Nutrition support has been given increasing focus in recent times. The issue in nutrition support is not only when to give and what to give, but also when not to give. Enteral nutrition should be preferred to parenteral nutrition and should be started within 24–48 h in critically ill patients [58]. Organ recovery was improved in patients in whom parenteral nutrition was postponed and there was evidence of increased autophagy in these patients [34]. Early nutrition also plays a key role in the post-operative period, contributing to a faster recovery of bowel function, without an increased risk of anastomotic leak [76].

Glutamine supplementation has been proposed to restore glutathione levels in critical patients, but the SIGNET and REDOXS trials did not show improvement in mortality, with the later even concluding that it increased mortality in patients with multiple organ dysfunction syndrome [26, 40].

Anemia of Critical Illness

In 176 patients admitted to a general ICU, 52% had a hemoglobin less than 9 g/dl, and a day later, this group had increased to 77%, yet none of these patients had history of bleeding or hematological disorders and neither chronic kidney disease. Hence, anemia is common in critical patients and it begins early on in the disease. It may develop into anemia of chronic disease and, although the underlying mechanisms differ, inflammation is the trigger in both situations [77]. This can be seen in the laboratory parameters, that change in the same direction, as shown in Table 2.

EPO, the main stimulus for red blood cell production, falls early on during acute disease. This fall in EPO has been suggested as a cause of anemia of critical illness (ACI), but this would take approximately 10 days to make a significant impact on hemoglobin concentration due to reduced red blood cell production. Nutrient deficiency has also been proposed, namely iron, but as iron is low in inflammation and ferritin is elevated, assessing for this deficiency proves difficult. Also, nutrient deficiency does not explain the significant increase in the prevalence of anemia at day 2 of admission [77]. Eryptosis and neocytolysis, both inhibited by EPO, have been suggested as causes, but no evidence that neocytolysis occurs in critical illness currently exists [33, 77]. There are other causes for ACI, such as fluid therapy or blood sampling, that may explain the further decline in the days following admittance to an ICU [77]. Vigorous fluid therapy, common to many critical patients, could have a low impact on ACI, as Pazarli and colleagues showed no relation between fluid balance and changes in hemoglobin [86].

There are no clear treatments for ACI, but general recommendations apply: limiting blood transfusions through a restrictive transfusion policy, minimizing blood sampling, and withholding drugs that may cause bone

Table 2. Characteristics of Anemia of Critical Illness (ACI) and Anemia of Chronic Disease (ACD) [77–85]

	ACI	ACD
Serum iron	↓	↓
Ferritin	↑	Normal/↑
Transferrin	↓	↓
Transferrin saturation	↓	↓
Soluble transferrin receptor concentration	Normal	Normal
Hypochromic red cells (%)	Normal/↑	Normal/↑
Erythropoietin concentration	Inappropriately low for degree of anemia (may be increased in acute renal failure)	Inappropriately low for degree of anemia
Iron deficiency	9% of patients	Common
Onset of fall in hemoglobin	Hours to days	Insidious
Expected hemoglobin levels	Variable, but can be lower than for ACD (< 9 g/dl in 52% of patients on ICU admission and 77% at day two of admission)	8–9.5 g/dl

marrow suppression [33, 77, 78]. Preventing its progression to anemia of chronic disease would certainly prove useful.

The Importance of Recognizing PICS and Frailty

Both patients in PICS and those who are frail have decreased physiologic reserve to go through a stress event without further compromising their physical status. One must focus on whether that patient will benefit from further treatment such as antibiotics in infectious illness. Antibiotics are regarded as a means to decrease fever and dyspnea; however, in hospice patients, antibiotics did not significantly contribute to relieve symptoms. Survival in those taking antibiotics did not differ from those in whom antibiotics were withheld [87]. The low physiologic reserve in these patients may make antibiotic therapy useless in face of inability to recover from the metabolic derangements that took place during the acute illness. Healthcare professionals must explain this to family members in order to obtain a shared decision between both parties.

Closing Remarks. Much remains to be known about inflammation and how its progresses thought the different phases presented. An understanding of this progress in a continuum would allow for future therapies to modulate the transition between these phases. Also, current treatments simply rely on catching up with the damages the inflammatory process is dealing. The catabolism generated by inflammation presents long-lasting consequences; hence, an adequate nutritional and non-nutritional support is imperative not only to limit the catabolism but also to avoid more oxidative stress. As presented, SIRS is not all equal, it depends on what caused and what is perpetuating it and much of the current knowledge and treatment is focused on the initial cause, like infection or pancreatitis. Further, there are no treatments aimed at CARS or PICS. There are still no biomarkers capable of distinguishing between the causes of SIRS. Inflammation must be seen as a potentially chronic event with acute-on-chronic exacerbations during the hospital stay and even beyond.

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COMPLIANCE WITH ETHICAL STANDARDS

Competing Interests. The authors declare that they have no competing of interest.

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