HLA-DR expression, cytokines and bioactive lipids in sepsis

Undurti Das

UND Life Sciences, Federal Way, USA

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Corresponding author:
Undurti Das MD
UND Life Sciences
2020, S 350th St, # K-202
98003 Federal Way
United States
Phone: 2162315548
E-mail: undurti@hotmail.com

Abstract

Sepsis accounts for more than 200,000 deaths annually in the USA alone. Both inflammatory and anti-inflammatory responses occur simultaneously in sepsis, the early phase dominated by the hyperinflammatory response and the late phase by immunosuppression. This late immunosuppression phase leads to loss of the delayed type hypersensitivity response, failure to clear the primary infection and development of secondary infections. Based on the available data, I hypothesize that failure to produce adequate amounts of inflammation resolving lipid mediators may be at the centre of both the hyperinflammatory response and late immunosuppression seen in sepsis. These proresolving lipids – lipoxins, resolvins and protectins – suppress exacerbated activation of leukocytes and macrophages, inhibit excess production of pro-inflammatory cytokines, initiate resolution of inappropriate inflammation, augment clearance of bacteria and other pathogens, and restore homeostasis. If true, this implies that administration of naturally occurring lipoxins, resolvins, protectins, maresins and nitrolipids by themselves or their more stable synthetic analogues such as 15-epi-16-(para-fluorophenoxy)-lipoxin A_4-methyl ester, a synthetic analogue of 15-epi-lipoxin A_4, and 15(R/S)-methyl-LXA_4 may form a new approach in the prevention (in the high-risk subjects), management of sepsis and in resolving the imbalanced inflammatory process such that sepsis is ameliorated early. In addition, recent studies have suggested that nociceptin and cold inducible RNA binding protein (CIRBP) also have a role in the pathobiology of sepsis. It is suggested that both nociceptin and CIRBP inhibit the production of lipoxins, resolvins, protectins, maresins, and nitrolipids and thus play a role in sepsis and septic shock.

Key words: sepsis, bioactive lipids, lipoxins, resolvins, protectins, maresins, nitrolipids, nociceptin, cold-inducible RNA binding protein, ghrelin.

Introduction

Sepsis, the systemic inflammatory response syndrome that occurs during severe infection, kills more than 200,000 people in the US annually [1]. Mortality in sepsis is due to multiple organ dysfunctions (MODS = multiorgan dysfunction syndrome) that cause death among patients in non-coronary critical care units. Thus, prognosis of patients with sepsis is related to the severity of organ dysfunction [2].

Several mechanisms contribute to the pathogenesis of MODS. Some of these include: bacterial toxins, inflammatory mediators secreted by neutrophils, macrophages, and T cells; endothelial injury, disturbed homeostasis, and microcirculatory failure. Sepsis impairs immune function by inducing defects in innate immunity and excessive lymphocyte apop-

tosis. Originally, it was believed that sepsis represents an uncontrolled inflammatory response. This led to clinical trials that studied the effect of agents that block the inflammatory cascade – corticosteroids, anti-endotoxin antibodies, tumor necrosis factor antagonists, and interleukin-1-receptor antagonists, all of which failed to reduce deaths due to sepsis. This questioned the original belief that death in patients with sepsis is due to uncontrolled inflammation.

Recent studies suggest that sepsis may present in the form of two distinct clinical syndromes, acute septic shock and severe sepsis. Acute septic shock syndrome occurs suddenly, the patient dying within 24–48 h, and is common in meningococcemia. Some, but not all, patients with septic shock develop severe sepsis. On the other hand, severe sepsis is characterized by signs of systemic inflammation and organ dysfunction, including abnormalities in body temperature, heart rate, respiratory rate and leukocyte count, elevated liver enzymes and altered cerebral function. Severe sepsis runs a protracted course over several weeks and patients succumb to the disease slowly. Autopsy of severe sepsis victims shows only minimal signs of inflammation or necrosis [3, 4]. Some patients with severe sepsis will subsequently develop septic shock. Thus, both severe sepsis and acute septic shock are two phases of the same syndrome and may occur in the same patient but at different periods of time indicating that the specific causative mediators of severe sepsis and septic shock are likely to be different. This may also explain why repeated attempts to develop new therapies for sepsis met with failure that is, in part, due to a lack of understanding of the pathogenic mechanisms driving sepsis. Thus, it is likely that sepsis is due to an initial exacerbated inflammatory response as a result of robust activation of the innate immune arm (pro-inflammatory), while the adaptive immune arm is being obliterated (immune suppression). It is now believed that the initial hyperinflammatory response subsequently leads to the progressive development of immunosuppression [5]. The duration of the initial hyperinflammatory response and subsequent immunosuppression is variable, which may impart the heterogeneous presentation(s) and responses seen in different subjects with sepsis. This implies that failure to suppress the inappropriate initial hyperinflammatory response and prevent subsequent immunosuppression could lead to failure to recover from tissue injury and/or damage to various target organs that may lead the patient to succumb. Depending on the severity and duration of these two well-studied and contrasting responses in sepsis will determine the variables noted in the clinical presentation of sepsis. One factor that is responsible for such variation(s) in the presentation of sepsis is mutations in Toll-like receptor 4 (TLR-4) [6, 7].

Common mutations in TLR-4 are associated with differences in lipopolysaccharide (LPS) responsiveness in humans, suggesting that gene-sequence changes alter host response to infections that could cause some to develop sepsis while others do not [6, 7]. This suggests that synthesis and release of adequate amounts of inflammation-resolving bioactive molecules may limit infection and injury and ensure recovery from sepsis. On the other hand, failure to produce adequate amounts of inflammation-resolving and tissue repair factors at the most appropriate time and stage of sepsis may prove to be fatal. In this context, it is noteworthy that TLRs regulate free radical generation as well as macrophage and leukocyte function and modulate eicosanoid synthesis, and thus play a critical role in inflammation and the immune response [8–10]. It is likely that initial excess stimulation of TLRs leads to exaggerated production of free radicals, pro-inflammatory eicosanoids and cytokines that produce the initial hyperinflammatory response which if followed by exacerbated negative feedback control could lead to progressive development of immunosuppression seen in sepsis. Thus, efforts to revert this initial hyperinflammatory response and subsequent immunosuppression may prove to be vital to initiate recovery from sepsis.

Toll-like receptors and bioactive lipids in sepsis

Polyunsaturated fatty acids (PUFAs) that form precursors to both pro- and anti-inflammatory lipid products modulate the expression of TLRs. For example, cyclooxygenase-2 (COX-2) mediated high production of prostaglandin E_2 (PGE_2) and, to a lesser extent, other prostanoids after LPS stimulation [11]. In contrast, LPS down-regulated COX-1 and COX-1 deficiency increased PGE_2 production following LPS stimulation in astrocytes [12]. Thus, LPS stimulated COX-2-dependent production of prostanoids, suggesting that coordinated down-regulation of COX-1 facilitates PGE_2 production after TLR activation [12, 13]. Supplementation of arachidonic acid (AA, 20 : 4 ω-6) and docosahexaenoic acid (DHA, 22 : 6 ω-3) reduced the incidence of necrotizing enterocolitis (NEC) and inhibited intestinal TLR-4 gene expression, and thus ameliorated NEC [14, 15]. Administration of resolvins and protectin D_1, which are derived from DHA and have potent anti-inflammatory actions, reduced the number of infiltrating leukocytes and blocked TLR-mediated activation of macrophages and suppressed interstitial fibrosis after ischemia-reperfusion-induced kidney injury [16, 17]. These results suggest that coordinated synthesis,

release and action of pro- and anti-inflammatory molecules control inflammation, lead to resolution of infection, and restore normalcy. This is supported by the observation that resolvin D_2, an anti-inflammatory compound derived from DHA, reduced excessive neutrophil trafficking to inflammatory loci, decreased leukocyte-endothelial interactions *in vivo* by endothelial-dependent nitric oxide production and direct modulation of leukocyte adhesion receptor expression and improved survival in a mouse model of microbial sepsis initiated by cecal ligation and puncture (CLP) [18].

Flavocoxid, a dual inhibitor of cyclooxygenase (COX-2) and 5-lipoxygenase (5-LOX), possesses antiinflammatory activity by reducing nuclear factor (NF)-κB activity and COX-2, 5-LOX and inducible nitric oxide synthase (iNOS) expression. In a murine model of CLP-induced polymicrobial sepsis, flavocoxid improved survival and reduced the expression of NF-κB, COX-2, 5-LOX, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), reduced blood leukotriene B_4 (LTB_4), PGE_2, TNF-α and IL-6, increased IL-10 production and lipoxin A_4 (LXA_4) serum levels, and protected against damage induced by CLP and reduced myeloperoxidase (MPO) activity in the lung and liver [19]. These results [18, 19] suggest that sepsis could be a pro-resolving deficiency disorder and methods designed to enhance the levels of anti-inflammatory bioactive lipids LXA_4 and resolvin D_2 might protect against sepsis and septic shock.

Cytokines, reactive oxide species and sepsis

A recent study by Toufekoula *et al.* [20] suggested that there is a close link between excess lipid peroxidation (measured as MDA) and specific organ failures in sepsis. They noted that lethal sepsis induced in rats by the intraperitoneal injection of a multi-drug resistance (MDR) isolate of *Pseudomonas aeruginosa* enhanced formation of lipid peroxidation products in greater amounts in the liver, spleen, and aortic wall, and it was lower in the kidney. These results matched those obtained in patients with sepsis; it was greater in patients with hepatic dysfunction and acute respiratory distress syndrome (ARDS) compared with patients without any organ failures. In contrast, the opposite was found for patients with acute renal dysfunction and no differences were found between patients with ARDS without or with cardiovascular (CV) failure and patients without any organ failure [20]. Serial measurements of MDA in serum of patients indicated that levels of MDA were greater in survivors of hepatic dysfunction and ARDS and lower in survivors of acute renal dysfunction. These results led to the conclusion that a compartmentalization of lipid peroxidation exists in systemic infections and perhaps MDA levels could be used as a prognostic marker to predict survival of sepsis. But, there appear to be more reliable markers to predict prognosis in sepsis compared to plasma MDA content [20].

Cytokines, HLA-DR expression and sepsis

Sepsis can be divided into two stages, acute septic shock and severe sepsis, as already discussed above [3, 4]. In animal models, sudden overproduction of TNF-α, as seen in human meningococcemia, triggers shock, circulatory collapse, renal and hepatic failure, and widespread inflammation and injury [21, 22]. Due to the rapid onset of TNF-α-mediated acute septic shock, there is insufficient time for adequate amounts of neutralizing anti-TNF-α antibodies to be generated. On the other hand, plasma concentrations of TNF-α are not increased in severe sepsis and administration of anti-TNF-α antibodies may actually worsen survival rates [23, 24]. Severe sepsis appears to involve HMGB1, a protein released by activated macrophages and monocytes that induces the release of other proinflammatory cytokines such as TNF-α, IL-1, and IL-6 [25, 26]. Although HMGB1 causes epithelial cell barrier dysfunction, lung injury, fever, and death, it does not produce shock. It is a potent inflammatory molecule, yet it produces only minimal pathological changes, similar to those associated with severe sepsis. Moreover, antibodies to HMGB1 have been shown to protect experimental animals against severe sepsis [25]. However, the role of HMGB1 and TNF-α in severe sepsis and acute septic shock in humans is still unsettled [27].

Severe sepsis is typically characterized by initial cytokine-mediated hyper-inflammation. Whether this hyper-inflammatory phase is followed by immunosuppression is a subject of controversy. Studies suggest that multiple immune defects occur in sepsis. In a study wherein sample of 40 patients who died with active severe sepsis were studied, it was noted that anti-CD3/anti-CD28-stimulated splenocytes from patients with sepsis, compared with those from controls, had significant reductions in cytokine secretion: TNF (5,361 pg/ml vs. 418 pg/ml); interferon-γ (1,374 pg/ml vs. 37.5 pg/ml); interleukin-6 (3,691 pg/ml vs. 365 pg/ml); and interleukin-10 (633 pg/ml vs. 58 pg/ml, taking 95% confidence interval into consideration) ($p < 0.001$ for all) [28]. Similar reductions in 5-hour lipopolysaccharide stimulated cytokine secretion were also noted. Cytokine secretion in patients with sepsis was generally less than 10% of that in controls, independently of age, duration of sepsis, corticosteroid use, and nutritional status. Flow cytometric analysis showed increased expression of selected inhibitory receptors and ligands and expansion of suppressor cell populations in

both spleen and lung [28]. Immunohistochemical staining showed extensive depletion of splenic CD4, CD8, and HLA-DR cells and expression of ligands for inhibitory receptors on lung epithelial cells. These bio-chemical, flow cytometric, and immunohistochemical findings are consistent with the hypothesis that immunosuppression occurs in patients with sepsis [28, 29].

In this context, it is noteworthy that free radicals generated by leukocytes, monocytes and macrophages in order to kill invading microorganisms also attack the cell membrane lipids, leading to the formation of lipid peroxides [30, 31]. In other words, the plasma concentrations of lipid peroxides reflect indirectly the amount of free radicals generated in a given instance. Since the half-life of free radicals is very short (a few seconds), while that of lipid peroxides is certainly longer than reactive oxygen species (ROS), it stands to reason that even after ROS production has subsided, the enhanced plasma levels of lipid peroxides are likely to persist for a longer time [32]. Early in the disease process, vigorous ROS generation may be desirable to restrain the infecting microorganisms. On the other hand, the persistence of increased ROS generation may be deleterious, as indicated by the association of ROS generation and increased SOFA score reported [33].

There is a close relationship between human leukocyte antigen (HLA)-DR and CD11b expression, free radical generation, and development and recovery from postoperative or post-trauma sepsis [34–36]. In patients with an uneventful recovery from severe trauma or surgery, the level of monocyte HLA-DR expression fell within hours of trauma or surgery, but returned to normal within a week [2, 34, 35]. In those who developed infection but recovered, 3 weeks were required for HLA-DR expression to return to normal. In contrast, in those who developed infection and sepsis and who died as a result, HLA-DR expression fell and never returned to normal. Similarly, after uncomplicated elective major abdominal surgery, expression of CD11b/CD18 (which is necessary for adhesion of neutrophils to endothelium) was unchanged throughout the postoperative period [34, 35]; in patients who developed postoperative sepsis, the expression of CD11b was significantly elevated within 24 h of surgery. Production of hydrogen peroxide by neutrophils followed a pattern similar to that of CD11b expression in these two groups of patients. Even production of hypochlorous acid (and possibly superoxide anion), a marker of neutrophil activation, was decreased in patients who had uncomplicated abdominal surgery as compared with those who developed sepsis 7–10 days later, in whom its production was augmented to supranormal levels on postoperative day 1 [36, 37]. It is interesting to note that these changes in HLA-DR and CD11b expression, hydrogen peroxide, and hypochlorous acid production were noted even when there was no evidence of infection. These results imply that persistence of enhanced free radical generation (and consequently enhanced lipid peroxidation) is harmful while maintenance of normal generation of free radicals is necessary to prevent infections and maintain normal function of various target organs such as liver, kidney and heart. Though these results appear to be apparently contrary to what was reported [20] with regard to MDA, one needs to take into consideration the half-life of lipid peroxides and free radicals. It is possible that enhanced levels of lipid peroxides detected [20] are a result of continuous production of physiologically relevant and necessary free radicals to abrogate infections that are expected to lead to generation of lipid peroxides that would eventually accumulate over a period of time due to their longer half-life compared to free radicals. Thus, a study correlating the generation of free radicals (superoxide anion, H_2O_2, HOCl and nitric oxide) by leukocytes and plasma levels of lipid peroxides and their relationship to monocyte HLA-DR expression is necessary to resolve this issue [27].

It appears that HLA-DR expression could serve as a reliable marker to predict outcome from sepsis. Wu *et al.* [38] and others [39–44] showed that persistent monocyte HLA-DR decreased expression was highly associated with the development of sepsis. Monocyte HLA-DR expression and flow cytometric measurement of plasma IL-6 and IL-10 by ELISA in 100 consecutive severely injured patients showed that a slope of monocyte HLA-DR expression (days 3–4/days 1–2) ≤ 1.1 and an IL-6 concentration ≥ 67.1 pg/ml remained highly associated with the development of sepsis (adjusted OR = 18.4, 95% CI: 4.9; 69.4, $p = 0.00002$), while IL-10 remained undetectable in most patients [43]. These results underscore the importance of daily monitoring of immune function in patients who are at high risk of sepsis to identify those who are likely to develop sepsis and also assess their prognosis [27].

It is noteworthy that an age-dependent increase in HLA-DR expression occurs in the population aged above 70 years and those aged above 70 years also have reduced secretion of inflammatory mediators TNF-α and IL-6 by peripheral blood mononuclear cells (PBMCs) and increased secretion of anti-inflammatory cytokine IL-10 after lipopolysaccharide (LPS) stimulation *in vitro* [41]. These results [45] coupled with those of Gouel-Chéron [43] suggest that there is a reciprocal relationship between HLA-DR expression on human PBMCs versus plasma IL-6 and IL-10 levels with advancing age, which seems to be altered in

those who develop sepsis. Furthermore, Abe *et al.* [46] noted that up-regulated IL-10 mRNA expression and diminished HLA-DR expression are indicators of poor outcome in those with sepsis. It was observed that peripheral leukocyte IL-10 mRNA expression measurement could predict the onset of immunoparalysis as indicated by diminished HLA-DR expression that occurs earlier than changes in IL-10 blood level, since it was reported that the degree of up-regulation of IL-10 mRNA expression during the first 24 h significantly correlated with the degree of diminished HLA-DR expression on day 3 ($r = 0.78$, $p < 0.001$). These [46] and other results [27–45] emphasize the importance of daily measurement of various cytokines, monocyte HLA-DR expression, free radical generation, lipid peroxides and possibly anti-oxidants in those who are critically ill to monitor, prognosticate and accordingly devise relevant treatment options. Despite these advances, sepsis still eludes a firm treatment regimen that leads to a predictive outcome and recovery. This suggests that there could be other mediators that play a critical role in the pathobiology of sepsis.

Sepsis as a pro-resolution deficiency disorder

Based on the preceding discussion, it is clear that timely development of inflammation and a heightened immune response characterized by appropriate free radical generation and cytokine release to ward off infection and initiation of resolution of inflammation, as well as suppression of the immune response in a sequential manner and gradient fashion, is essential to prevent the development of sepsis, initiate or enhance wound healing and resolve inflammation.

According to the above, I hypothesize that in sepsis and other systemic inflammatory conditions, there could occur not only an increase in pro-inflammatory molecules such as IL-6, TNF-α, HMGB1, prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs), isoprostanes, trans-fatty acids and free radicals but also a deficiency in the production and action of anti-inflammatory molecules such as IL-4, IL-10, lipoxins, resolvins (LXs), protectins, maresins and nitrolipids. This is supported by the observation that lipopolysaccharide (LPS) or platelet activating factor (PAF)-induced intravascular volume loss (microvascular fluid leak) was attenuated by LXA_4 [47]. In a cecal ligation and puncture (CLP) model of sepsis, when LXA_4 (40 µg/kg, *i.p.*) 5 h after surgery was given, it increased 8-day survival and attenuated tissue injury after 8 days. Plasma IL-6 (a pro-inflammatory cytokine), monocyte chemotactic protein 1, and IL-10 (an anti-inflammatory cytokine) levels were reduced in LXA_4-treated rats compared with controls. Lipoxin A_4 reduced nuclear factor κB (NF-κB) activation in peritoneal macrophages, reduced blood bacterial load and increased peritoneal macrophage number without affecting phagocytic ability, suggesting that LXA_4 reduced blood bacterial load by enhancing macrophage activation and that LXA_4 increased survival in sepsis by simultaneously reducing systemic inflammation as well as bacterial load [48]. Thus, lipoxins, resolvins, protectins, and maresins that are lipid mediators may serve as stereoselective players that counter-regulate excessive acute inflammation and stimulate molecular and cellular events that induce resolution of inflammation.

This implies that changes observed in HLA-DR expression, cytokine alterations, free radical generation and lipid peroxides noted in sepsis are likely due to an inappropriate inflammatory process and deficiency of anti-inflammatory bioactive lipids, lipoxins, resolvins, protectins, maresins and nitrolipids [49, 50] (see Figure 1). In this context, it is interesting to note that Bannenberg *et al.* [49] while studying the cellular events underlying the resolution of acute inflammation in a murine peritonitis model noticed that the onset of resolution of inflammation was at 12 h and eicosanoids and PUFAs first appeared within 4 h of onset of inflammation. It was noted that the DHA-derived anti-inflammatory lipid mediator 10,17S-docosatriene was generated during the resolution interval that occurred between the time when maximal neutrophil infiltration occurs during inflammation and when neutrophil numbers reach half, whereas LXA_4, resolvin E_1 and 10,17S-docosatriene participated in the activation and/or accelerated resolution of inflammation [49]. For example, LXA_4 or aspirin-triggered LXA_4 analogue reduced the maximal neutrophil numbers that are present during inflammation; resolvin E_1 decreased both the number of neutrophils infiltrating and the time of their maximal accumulation; whereas 10,17S-docosatriene reduced the number of neutrophils infiltrating and the time of their maximal accumulation and shortened the time needed for resolution of inflammation (that is, resolution occurred early) [49, 50]. Furthermore, LXA_4 inhibited the production and accumulation of pro-inflammatory cytokines and chemokines (20–50% inhibition) at the end of 4 h of initiation of inflammation, while the effect of resolvin E_1 and 10,17S-docosatriene on cytokines and chemokines was maximal at 12 h (30–80% inhibition) [49, 50]. In addition, LXA_4 evoked the release of anti-phlogistic cytokine TGF-β (transforming growth factor-β). These results suggest that LXA_4, resolvin E_1 and 10,17S-docosatriene (protectin) act in a symmetrically orchestrated fashion, each having a specific action on the resolution phase of the inflammatory process (for example, LXA_4 decreases the infiltration of neutrophils to the inflamma-

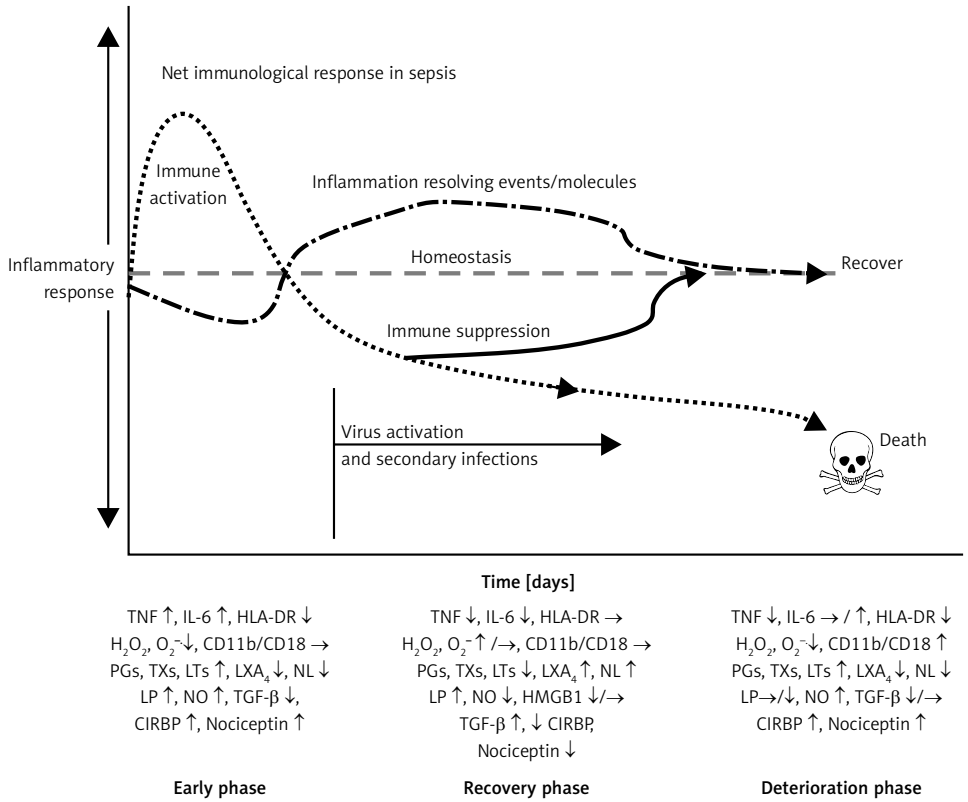

Figure 1. Inflammatory and immune response in sepsis over time. Both pro- and anti-inflammatory responses are activated early in sepsis. But, in the initial stages the pro-inflammatory response predominates. As sepsis progresses, the anti-inflammatory and immunosuppressive response becomes dominant during which secondary infections and dormant viral activation are likely to occur. Early deaths during the initial stages of sepsis are due to the pro-inflammatory response that leads to cytokine storm, whereas later deaths are due to immunosuppression that leads to failure to control opportunistic infections and other pathogens. In the early phase of sepsis, TNF-α, IL-6, H_2O_2, O_2^{-}, PGs, TXs, LTs, LP (lipid peroxides) and NO tend to be high, whereas LXA_4, resolvins and protectins and TGF-β will be lower. As the sepsis progresses and immunosuppression phase sets in, TNF-α, IL-6, H_2O_2, O_2^{-}, PGs, TXs, LTs, LP (lipid peroxides) and NO remain high and LXA_4, resolvins and protectins and TGF-β continue to be lower and are not produced in sufficient amounts to initiate resolution of sepsis. In those in whom sepsis starts to resolve or is likely to subside, TNF-α, IL-6, H_2O_2, O_2^{-}, PGs, TXs, LTs, and NO revert to normal levels or fall to lower levels compared to the early phase of sepsis whereas LP may remain higher while LXA_4, resolvins and protectins and TGF-β increase to initiate resolution of sepsis and restore normal health. It is likely that nociceptin, CIRBP and ghrelin also modulate the synthesis of bioactive lipids and thus play a role in sepsis.

NO – nitric oxide, NL – nitrolipids, PGs – prostaglandins, TXs – thromboxanes, LTs – leukotrienes, LP – lipid peroxides, CIRBP – cold-inducible RNA binding protein

tory site; resolvin E_1 decreases both the number and time of neutrophil infiltration; while 10,17S docosatriene not only decreases the number and time of neutrophil infiltration but also enhances the resolution phase of inflammation) [49, 50]. The ability of LXA_4 to enhance the release of TGF-β in addition to inhibiting the production of pro-inflammatory cytokines and chemokines at the end of 4 h after initiation of the inflammatory process while similar actions by resolvin E_1 and 10,17S-docosatriene at the end of 12 h after the initiation of the inflammatory process indicates that these bioactive lipids act in concert with each other in a phased but orchestrated fashion such that the initiation of the inflammatory resolution process is initiated by LXA_4 and continuation of the resolution process is maintained by resolvin E_1 and 10,17S-docosatriene [49, 50]. It is interesting to note that resolvins and protectins (including 10,17S-docosatriene) may play a role in clearance of the debris of inflammation including dead neutrophils and T cells by macrophages [50, 51]. Thus, lipoxins, resolvins, protectins and nitrolipids have anti-inflammatory and pro-resolution properties, thereby protecting organs from collateral damage, stimulating the clearance of inflammatory debris and promoting mucosal antimicrobial defense [49–55] (see Table I for summary of their actions).

In view of this, it is worthwhile to measure plasma and, wherever feasible, urinary and other body fluid concentrations of pro- and anti-inflammatory cytokines, various PGs, TXs, LTs, isoprostanes, trans-fatty acids, lipoxins, resolvins and protectins, maresins, and nitrolipids to specifically determine their dynamic alterations at various stages of the illness (see Table II). Such a study

Table I. Brief summary of actions of lipoxins, resolvins, protectins and nitrolipids as applicable to their role in sepsis. Many more actions of these compounds are being discovered and are possible; only those that are relevant to sepsis are given

Name	Role
Lipoxins (LXA_4 and ATL = aspirin-triggered lipoxin A_4)	Anti-inflammatory, reduce neutrophil infiltration, suppress cytokine and chemokine secretion, free radical generation, stop chemotaxis, adherence and transmigration, reduce CD11b/CD18 expression, inhibit peroxynitrite generation, attenuate AP-1, NF-κB accumulation, stimulate nonphlogistic phagocytosis of apoptotic neutrophils, stimulate endothelial nitric oxide generation, inhibit VEGF-induced endothelial-cell migration and angiogenesis, inhibit leukotriene secretion and action, inhibit peroxynitrite generation, enhance TGF-β production
Resolvins	Anti-inflammatory, enhance wound healing, stop transepithelial and transendothelial migration, stimulate nonphlogistic phagocytosis of apoptotic neutrophils, enhance debris removal by macrophages, inhibit cytokine and chemokine secretion, decrease neutrophil number and duration of neutrophil infiltration at the site of inflammation
Protectins (including 10,17S-docosatriene)	Upregulate CCR5 expression (lipoxins and resolvins also have this property), stimulate nonphlogistic phagocytosis of apoptotic neutrophils by macrophages, inhibit production of pro-inflammatory cytokines, promote apoptosis, decrease the number and duration of neutrophil infiltration at sites of inflammation and enhance resolution phase of inflammation, have cytoprotective properties, inhibit NF-κB and cyclooxygenase-2 induction
Nitrolipids	Nitration reactions can occur with all unsaturated fatty acids (PUFAs) and can be detected in urine and blood, serve as ligands for PPARs and thus modulate metabolic and cellular differentiation genes, regulate inflammatory responses, adipogenesis, glucose homeostasis and systemic inflammatory responses (including sepsis), possess anti-inflammatory action, prevent platelet activation, inhibit LPS-induced secretion of pro-inflammatory cytokines in macrophages, produce vascular relaxation, inhibit neutrophil degranulation and superoxide formation

would not only lead to a better understanding of the inflammatory process but would also help to elicit the exact role of cytokines and bioactive lipids (including nitrolipids) [55] in various stages of illness and how their alterations are associated with different clinical indices.

On the basis of the above, I hypothesize that administration of anti-inflammatory bioactive lipids, lipoxins, resolvins, protectins and maresins by themselves or their synthetic analogues (including those of nitrolipids) to suppress inappropriate inflammation and initiate resolution of the target tissue/organ damage in sepsis should be considered seriously. Lipoxins, resolvins, protectins and nitrolipids could be coupled to human albumin to stabilize them, and albumin, in turn, is expected to release these bioactive lipids slowly for the management of sepsis and other critical illnesses.

In addition to the role of cytokines and bioactive lipids, recent evidence suggests that ghrelin, nociceptin and cold-inducible RNA binding protein (CIRBP) also play a significant role in sepsis [56–59] (Table II). For instance, ghrelin, a growth hormone secretagogue produced by the gut, not only plays an important role in the regulation of appetite, energy balance and glucose homeostasis but also possesses anti-bacterial activity, suppresses pro-inflammatory cytokine production and restores gut barrier function. In experimental animals, ghrelin prevented mortality from sepsis. Thus, the ability of the gut to produce ghrelin could serve as an endogenous protective function to suppress inflammation. It is predicted that ghrelin may enhance the production of lipoxins, resolvins, protectins, maresins and nitrolipids [56] (Figures 1 and 2).

A recent study showed that plasma nociceptin concentrations increased during an episode of sepsis in comparison to those who were recovering from the illness [57], a pattern that was similar to the changes seen with pro-inflammatory cytokines. This indicates that enhanced plasma levels of nociceptin indicate continuation of the sepsis process [58] whereas a decrease in their levels may indicate recovery.

Increased levels of CIRBP in the blood of subjects with hemorrhagic shock and in animal models of hemorrhage and sepsis have been reported [59]. CIRBP stimulated the release of TNF-α and HMGB1 from macrophages, induced the inflammatory response and produced tissue injury when injected *in vivo*. In contrast, CIRBP-deficient mice were found to be resistant to the induction of lethality by TNF-α and HMGB1. The CIRBP seems to mediate its inflammatory actions by acting on Toll-like receptor 4 (TLR4)-myeloid differentiation factor 2 (MD2) complex. These studies led to the conclusion that CIRBP plays a role in shock and sepsis [59]. If the proposal presented here is correct, it implies that nociceptin, ghrelin and CIRBP have a modulatory role in the production of lipoxins, resolvins, protectins, maresins and nitrolipids

Table II. Scheme showing bioactive lipids, cytokines, ghrelin and other mediators that could be measured at various time points in patients with sepsis and correlated with prognosis. Adopted from ref. no. [49] and modified. These bioactive lipids/cytokines and other compounds could also be measured in urine at different time points and correlated with their plasma levels and prognosis of the patient. Though not mentioned in the table, other measurements that could be performed include: lipid peroxides, nitric oxide, anti-oxidants (such as SOD, glutathione, catalase) and A-FABP

Source of body fluid/tissue	Bioactive lipids to be measured	Time at which measured in sepsis/critically ill	Method of measurement	Likely change
Plasma	PUFAs: LA, GLA, DGLA, AA, ALA, EPA, DHA and their trans-fatty acids	On admission, every 24 h until discharge or death	GC; LC-MS	GLA, AA, EPA and DHA ↓ at admission; restored to normal if appropriate external supplementation is given; trans-fatty acids ↑ at admission, will decrease if inflammation is contained and indicates relatively good prognosis
Plasma	Various PGs, LTs, TXs	On admission, every 24 h until discharge or death	ELISA-HPLC	↑ in 2 series PGs, TXs, 4 series LTs indicates inflammatory process is dominant; ↑ in 3 series PGs, TXs, 5 series LTs indicates that the administered EPA is being converted to these products; to be correlated with levels of lipoxins, resolvins, protectins and maresins; ↓ in 2 series PGs, TXs, 4 series LTs after GLA/EPA/DHA supplementation indicates decreasing tendency of inflammation
Plasma	Lipoxins, resolvins, protectins, maresins	On admission, every 24 h until discharge or death	LC-MS	Lipoxins, resolvins, protectins, maresins ↓ at admission, restored to normal if patient is improving, remain low if prognosis is poor
Plasma	Nitrolipids	On admission, every 24 h until discharge or death	LC-MS/MS-MS	Nitrolipids ↓ at admission, restored to normal if patient is improving, remain low if prognosis is poor
Plasma	Isoprostanes	On admission, every 24 h until discharge or death	LC-MS/MS-MS	Isoprostanes ↑ at admission, restored to normal if patient is improving, remain high if prognosis is poor
Plasma	Cytokines	On admission, every 24 h until discharge or death	ELISA and/or flow cytometric-based immunofluorescence assays	If pro-inflammatory cytokines are ↑ – it indicates inflammation is dominant; if anti-inflammatory cytokines are ↑ it indicates recovery process is on the anvil; correlation needs to be made among cytokine profile, bioactive lipids and clinical picture
Plasma	Ghrelin	On admission, every 24 h until discharge or death	ELISA	Ghrelin levels may correlate with IL-6 and TNF-α; if ghrelin levels are decreased it indicates inflammation is dominant, gradual increase in ghrelin levels indicates recovery from sepsis and restoration of gut barrier function
Plasma	Nociceptin and CIRBP	On admission, every 24 h until discharge or death	ELISA	Nociceptin levels may correlate with IL-6 and TNF-α; an increase in nociceptin levels indicates inflammation is dominant, gradual decrease in its levels indicates recovery from sepsis. CIRBP may show response similar to nociceptin

LA – linoleic acid, GLA – γ-linolenic acid, DGLA – dihomo-GLA, AA – arachidonic acid, ALA – α-linolenic acid, EPA – eicosapentaenoic acid, DHA – docosahexaenoic acid, PGs – prostaglandins, TXs – thromboxanes, LTs – leukotrienes, SOD – superoxide dismutase, A-FABP – adipose-fatty acid binding protein, CIRBP – cold-inducible RNA binding protein

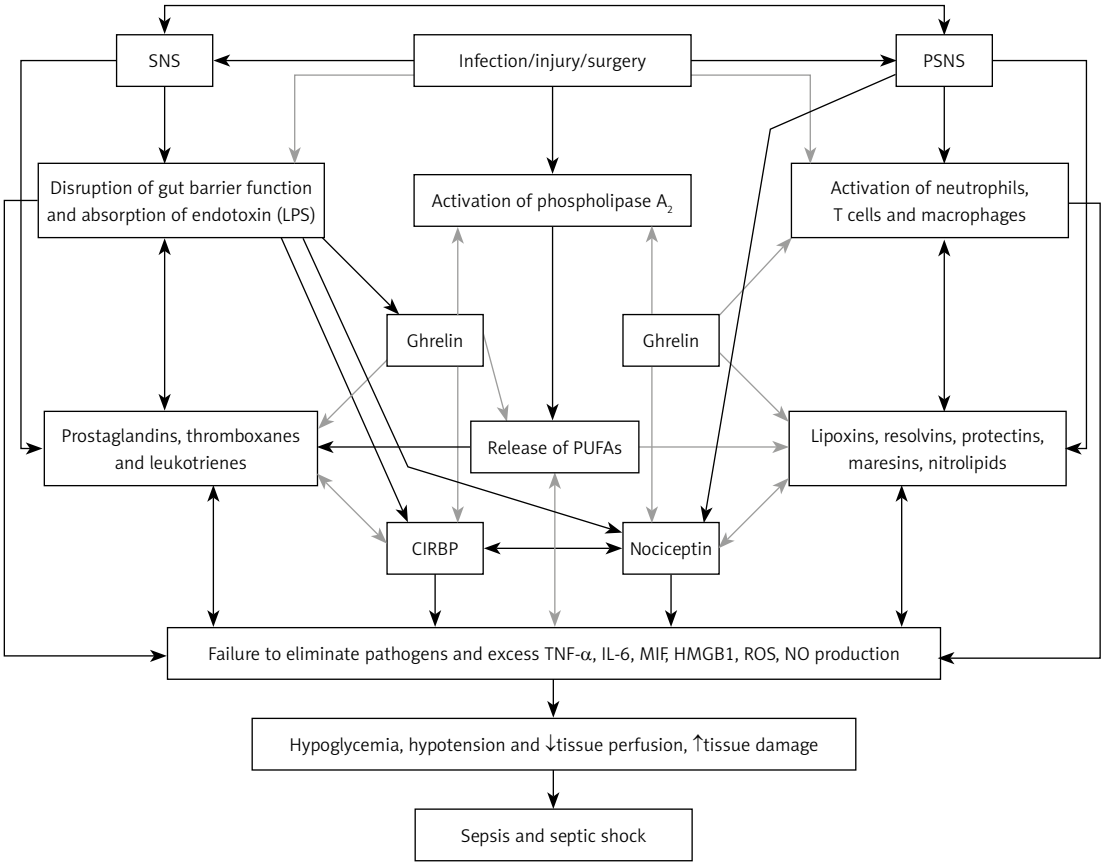

Figure 2. Scheme showing relationship among infection, LPS, PUFAs, eicosanoids, cytokines, ROS and sepsis and septic shock. During infection/injury/surgery (especially following abdominal surgery), gut barrier function is disrupted leading to the absorption of endotoxins (LPS) from the gut into the circulation. The LPS activates monocytes, macrophages and leukocytes leading to release of the pro-inflammatory cytokines TNF-α, IL-6, MIF and HMGB1 that, in turn, incite excess production of free radicals, nitric oxide and pro-inflammatory eicosanoids (prostaglandins, thromboxanes and leukotrienes), which lead to hypoglycemia, hypotension, decreased tissue perfusion and tissue injury, resulting in sepsis and septic shock. Lipoxins, resolvins, protectins, maresins and nitrolipids have anti-inflammatory actions, suppress production of TNF-α, IL-6, MIF, HMGB1, free radicals, inducible nitric oxide and pro-inflammatory eicosanoids, restore gut barrier function, eliminate invading micro-organisms, and suppress the activation of macrophages and leukocytes, and thus are of benefit in sepsis and septic shock. In addition, LPS stimulation of monocytes, macrophages and leukocytes enhances the secretion of cold-inducible RNA binding protein (CIRBP) and nociceptin, both of which enhance production of TNF-α, IL-6, MIF and HMGB1 that, in turn, lead to the onset and progression of sepsis and septic shock. It is predicted that based on the current hypothesis both CIRBP and nociceptin inhibit the production of lipoxins, resolvins, protectins, maresins and nitrolipids, whereas the latter inhibit the production and action of CIRBP and nociceptin. Ghrelin, a growth hormone secretagogue produced by the gut, which plays an important role in the regulation of appetite, energy balance and glucose homeostasis, has been shown to possess anti-bacterial activity, suppress pro-inflammatory cytokine production and restore gut barrier function. In experimental animals, ghrelin prevented mortality from sepsis. Thus, production of ghrelin by the gut could be a protective phenomenon to suppress inflammation. It is predicted that ghrelin enhances the production of lipoxins, resolvins, protectins, maresins and nitrolipids. Hence, it is important to study the interactions among LPS, cytokines, ghrelin, CIRBP, nociceptin, various eicosanoids and lipoxins, resolvins, protectins, maresins and nitrolipids and their role in sepsis and septic shock. For further details see the text

(Figures 1 and 2). It is likely that ghrelin enhances the synthesis of these bioactive lipids whereas nociceptin and CIRBP suppress their production, a suggestion that needs to be proved.

Conclusions

Sepsis accounts for a considerable number of deaths in critical care units throughout the world. There is reasonable evidence to suggest that the duration(s) of the initial hyperinflammatory response and subsequent immunosuppression is variable in different subjects with sepsis, which may account for its variable presentation [5]. It is likely that the coordinated synthesis, release and action of pro- and anti-inflammatory molecules that control inflammation, resolve infection, and restore normalcy matching with the underlying pathophysiology of sepsis are missing, which leads to mortality. Until now, emphasis has been on inflammatory events with little attention being paid to resolution of inflammation. In the present hypothesis, I propose that failure of the produc-

tion of adequate amounts of anti-inflammatory molecules such as lipoxins, resolvins, protectins, maresins and nitrolipids that trigger pro-resolution events could be responsible for the continuation and failure of resolution of inflammation and onset of sepsis. This hypothesis can be verified by estimating plasma and urinary (and possibly, other body fluids) concentrations of lipoxins, resolvins, protectins, maresins and nitrolipids in addition to the measurement of both pro- and anti-inflammatory cytokines including nociceptin, CIRBP, ghrelin and natriuretic peptides [60] and correlating their levels with the stage and severity of sepsis as depicted in Figures 1–2 and Tables I–II. The clinical application of this hypothesis is that lipoxins, resolvins, protectins, maresins, nitrolipids and ghrelin and/or their more stable synthetic analogues could prove to be useful in the prevention and management of sepsis. In this context, it is interesting to note that statins that have been shown to be of use in sepsis [61] are known to enhance the synthesis of lipoxins [62, 63].

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