Aging and Disease
www.aginganddisease.org
Volume 2, Number 6; 501-511, December 2011

Review

Effects of Aging on Inflammation and Hemostasis through the Continuum of Critical Illness

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[Received June 6, 2011; Revised October 2, 2011; Accepted October 5, 2011]

ABSTRACT: Older age has long been associated with altered inflammation and hemostasis regulation. Emerging evidence suggests that age-related differences in inflammation and hemostasis abnormalities may play a role in the development of and long-term outcomes after critical illness. A better understanding of underlying mechanisms may provide new possibilities for therapeutic interventions. In this review, we will examine how age-related differences in inflammatory and coagulation responses are affected through the continuum of healthy state, before infection occurs, to severe sepsis and recovery.

Key words: Aging; Infection; Sepsis; Inflammation; Coagulation

Older age has long been associated with altered inflammatory and hemostasis regulation [1, 2]. For example, chronic elevation of inflammatory and hemostasis markers has been implicated in a number of age-related chronic conditions, such as frailty syndrome, Alzheimer's disease, and atherosclerosis [3, 4]. The effects of age-related inflammatory and hemostasis dysregulation on critical illnesses, such as sepsis, remains incompletely understood.

Classically, sepsis has been characterized by an exuberant immune response, reflected in many-fold higher levels of inflammatory and hemostasis markers. Given the well known higher mortality seen in older adults, it has been suggested that sepsis in the elderly is driven by an age-related increase in inflammation. Recently it has been hypothesized that sepsis may also be characterized by an exuberant anti-inflammatory or immunosuppressive phase that occurs after the initial inflammatory burst [5, 6]. Unfortunately, clinical studies have failed to confirm these hypotheses. The complexity of the immune response in sepsis has befuddled clinicians and scientists alike and underscores the many failed therapeutic trails to date.

Understanding the potential effects of aging on the inflammatory and hemostasis response before, during, and after sepsis is important to design appropriate prevention and treatment strategies for the elderly. In this article, we will examine how age-related differences in inflammatory and coagulation responses are affected through the continuum of healthy state, before infection occurs, to severe sepsis and recovery.

Inflammation and hemostasis as markers of immune response

Clinical and experimental models of sepsis often measure circulating inflammatory and hemostasis cytokines/chemokines as markers of immune activity. There exist other biologic processes of systemic inflammation, however, such the stress triggered inflammatory system mediated by the hypothalamic-pituitary-adrenal axis, and are reviewed elsewhere [7]. The immune system is divided into the innate response and the adaptive response. The innate response comprises the initial recognition and destruction of pathogens and is characterized by its rapid action and lack of immunologic memory. It is triggered by the recognition of a pathogenic antigen by Toll-like receptors on circulating immune cells. This results in the

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ISSN: 2152-5250

activation of transcription factor NF-kB, a "nodal point" linking pathogen recognition to immune response [2]. The NF-kB system is considered the master regulator of the innate immune system and leads to the production of pro-inflammatory cytokines such as TNF and IL-6 that are crucial to activating downstream cytokines, recruiting immune effector cells, activating coagulation networks, and stimulating the adaptive immune response. Adaptive immunity differs from innate immunity in its ability to form an immunologic memory and thereby adapt its response to previously encountered pathogens. Upon elimination of the pathogen, mechanisms to resolve the immune response are activated to prevent unintended harm to the host. Such mechanisms include the prostaglandin network and the activated glucocorticoid receptor, the latter of which stimulates production of glucocorticoids that counteract the effects of activated NF-kB [8-10]. Both the initiation and resolution of the immune response are highly coordinated, active processes.

Sepsis in the elderly

Sepsis, the 10th leading cause of death in the elderly, refers to the presence of at least two systemic inflammation response syndrome criteria (fever or hypothermia, tachycardia, increased respiratory rate, and elevated leukocyte count) in the presence of infection. Most adult patients with an infection serious enough to require hospitalization are septic. Respiratory tract infections, such as community-acquired-pneumonia (CAP), are the leading cause of sepsis in developed countries [11]. When sepsis is complicated by organ failure, it is called severe sepsis and is a grave prognostic indicator. For instance, 90-day mortality after CAP is 6%, whereas mortality approaches 26% for patients who develop severe sepsis, and the mortality approaches 40% for the subset that develop septic shock [12].

Severe sepsis is a disease of the elderly. In a large epidemiologic study, Angus, et al. showed that approximately 750,000 people per year develop severe sepsis in the U.S., with a mean age of 63.8 years [11]. The incidence increases exponentially with age, and hospitalization rates for severe sepsis in those ≥ 80 years were approximately 2-fold, 6-fold, and 15-19 fold higher than those 65-79yr, 50-64yr, and 35-49 years, respectively [13, 14]. The higher incidence of severe sepsis in the elderly is likely due to a higher risk of infection and a higher risk of organ dysfunction once infection occurs.

The incidence rates of severe sepsis have increased over the past 2 decades, likely due to the aging of the population and an increased number of older adults with chronic diseases, prosthetic devices, and immunosuppressive states. Martin et al. found that, from 1979-2000, the average incidence of sepsis increased 11.5% per year in those ≥ 65 years compared to 9.5% per year in those < 65 years [14]. The true incidence rate may be higher, since sepsis is a clinical diagnosis and the elderly typically exhibit blunted signs of infection.

Older age is also an independent risk factor for mortality among adults hospitalized with sepsis. Between 1979-2002, case fatality increased linearly across age deciles and averaged 27.7% for those ≥ 65 years compared to 17.7% for those < 65 years [14]. In a recent prospective cohort study of patients hospitalized with pneumonia-induced sepsis, we found an age-related increase in in-hospital, 90-day, and 1-year post-discharge mortality (Figure 1) [6].

The reason for the higher susceptibility to infection, and once infection occurs, the higher risk of severe sepsis in older adults remains unclear. Epidemiologic studies suggest that age-related differences in clinical risk factors, such as chronic disease burden and higher rates of institutionalization in the elderly, help to explain some, but not all, of these differences [15]. Another factor may be immunosenescence, or the age-related subclinical changes in the innate and adaptive immune response, which may increase the risk of severe sepsis and subsequent mortality. To this end, we will focus on how age-related inflammation and hemostasis, two interrelated and well-studied components of the immune response, act as markers of overall immune activity and examine its role in the incidence, severity, and long-term outcomes of sepsis.

Role of inflammation and hemostasis in susceptibility to infection

Older age is associated with chronically elevated circulating levels of inflammatory markers such as interleukin (IL)-6, tumor necrosis factor (TNF), IL-1 receptor antagonist, and C-reactive protein (CRP) [2, 16]. Although chronic inflammation is associated with several chronic diseases, plasma levels of IL-6 have been shown to be associated with increased age, independent of chronic disease states [17]. Increased inflammatory markers in older adults are on average 2-4 fold higher than in younger adults. In contrast, inflammatory markers are several log-fold higher during sepsis compared to levels observed in the absence of infection, regardless of age.

Aging is also associated with a pro-thrombotic state, in part due to activation of hemostasis networks by

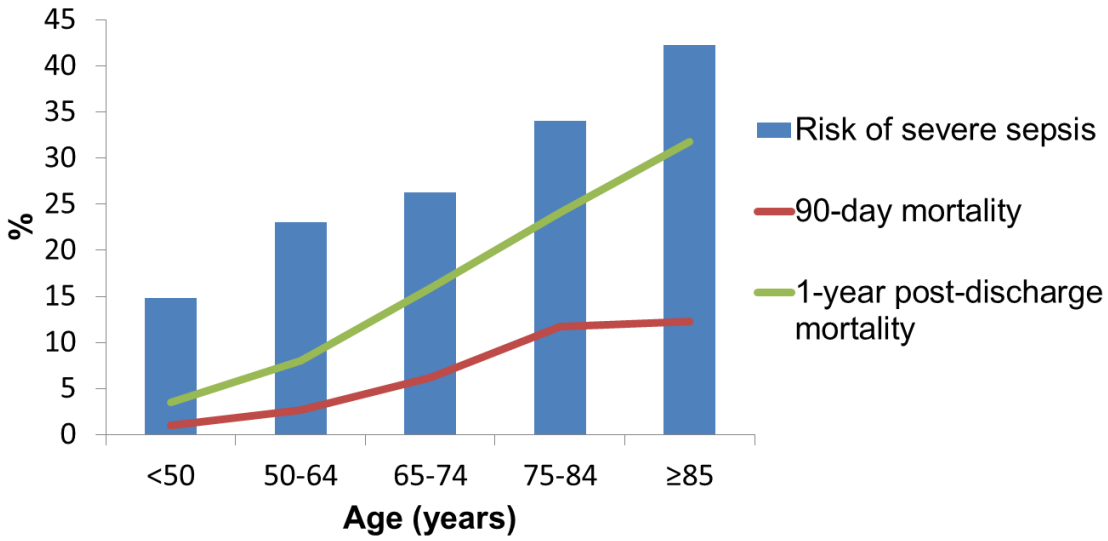

Figure 1. Age-stratified risk of severe sepsis and mortality rates from a prospective cohort study of adults hospitalized with community-acquired pneumonia. 90-day mortality measured from day of hospital admission. 1-year post-discharge mortality measured from day of hospital discharge. All rates increased significantly across age groups (P<0.001).

inflammatory cytokines. Older adults exhibit increased levels of fibrinogen, F-VII, F-VIII and other clotting factors [18, 19]. In a study of 1729 subjects ≥ 70 years, high D-dimer levels were found in 7% of those 70-79 years, 13% of those 80-89 years, and 23% of those 90-99 years [20]. Clinically, this pro-thrombotic state may explain the age-related increased risk of venous thrombosis, atherosclerosis, and pulmonary emboli [19, 21].

The reasons for increased inflammation and coagulation in older adults are unclear and likely multifactorial [22]. It has been proposed that latent infections, such as cytomegalovirus (CMV), which are prevalent in up to 80% of older adults, may act as chronic stimuli of the inflammatory system [23, 24]. There is also growing research into the role oxidative stress in creating pro-inflammatory states [25]. Aging is associated with increased pro-inflammatory prostaglandins such as cycloxygenase and lipooxygenase. During aging, anti-oxidant systems decline, leading to an imbalance in redox status and activation of redox-sensitive transcription factor NF-kB [2]. Activation of NF-kB leads to the expression of pro-inflammatory mediators, including TNF and IL-6, as well as upregulation of adhesion molecules [25, 26].

Regardless of its causes, a pro-inflammatory milieu can serve as a risk factor for infection in at least two ways. First, persistent activation of B and T lymphocytes by inflammatory cytokines is thought to extinguish the replicative potential of immune cells [27]. For example, T cells of patients with inflammatory syndromes such as rheumatoid arthritis and chronic infections, including CMV, have shortened telomeres, indicative of extensive replication, and decreased T cell receptor repertoire. These changes are also characteristic of T cell aging and limit the ability of the adaptive immune system to respond to novel antigens [28].

Persistent inflammation has been shown to increase risk of bacterial invasion in rodent models. Systemic administration of TNF in rats before inoculation of bacteria into the lungs worsens pneumonia by reducing alveolar neutrophil recruitment and bacterial clearance [29, 30]. A critical step during the process of bacterial invasion is the adherence of bacteria to host cell surfaces. Recent studies show that two receptors common on many cell types, polymeric immunoglobulin receptor (pIgR) and platelet activating factor receptor (PAFr), are vulnerable to bacterial attachment [31, 32]. Mice lacking PAFr as well as those treated with PAFr antagonists are resistant to invasive pneumococcus [33, 34]. Both pIgR and PAFr are upregulated by transcription factor NF-kB. Cells in acute and chronic states of inflammation have been found to express increased pIgR and PAFr and are bound by S.

pneumoniae more often than resting cells. Using a mouse model, Hinojosa and colleagues recently sought to determine if chronic, low-grade inflammation in mice would cause increased levels of pIgR and PAFr in the lung and increased susceptibility to pneumonia [35]. Young mice, when infused systemically with low levels of TNF for up to 6 days, had increased lung pIgR and PAFr protein levels and a susceptibility to pneumococcal pneumonia that was higher than young mice controls and on par with sham old mice.

Epidemiologic studies also suggest that increases in inflammation may increase the susceptibility to infection. For instance, we have previously shown that chronic inflammation is a risk factor for hospitalization with pneumonia in otherwise healthy older adults. In a cohort of well-functioning older adults 70-79 years, the highest tertiles of circulating TNF and IL-6 were associated with a higher risk of pneumonia independent of coexisting medical conditions, smoking status, or use of steroid medication [36]. Whether the small differences in circulating cytokine levels and the increased risk of serious infection observed in clinical studies constitutes a cause-effect relationship or is simply a marker for other immune defects are unclear.

Role of inflammation and hemostasis response during sepsis

A dysregulated immune response has been suggested to play an important role in the progression of sepsis to severe sepsis, and clinical trials have focused on modulating the immune response by targeting different inflammatory molecules. Epidemiologic and animal studies have shown that higher circulating inflammatory cytokines, such as IL-6, are associated with increased risk of severe sepsis and mortality [37-39]. The inflammatory response also activates, and is in turn activated by, the coagulation response and diminished fibrinolysis [40]. This promotes vascular leakage, vasodilation, microvascular dysfunction, and increases the risk of organ hypoperfusion and downstream ischemia.

While higher systemic levels of inflammation and coagulation are associated with multiple organ failure and death, several lines of evidence suggest that severe sepsis is a heterogeneous condition. For example, trials using limited duration anti-TNF strategies have failed to improve outcomes [41]. Recent evidence from well-designed epidemiologic studies have shown that, while higher pro-inflammatory and hemostasis levels are associated with organ failure and mortality, these abnormalities are present in many patients who do not develop organ dysfunction. In a large, multicenter inception cohort of 2320 subjects enrolled upon presentation to the emergency department with CAP, a broad panel of inflammatory (TNF, IL-6, IL-10) and coagulation markers (D-dimer, antithrombin, F-IX, thrombin-antithrombin complex, plasminogen-activator inhibitor-1) were measured daily for the first week and weekly thereafter [42]. Although increasing levels of inflammatory markers on day 1 were associated with increased risk of severe sepsis and mortality, the differences in inflammatory profile between survivors and non-survivors were modest. Furthermore, the onset of organ dysfunction was not associated with an increase in cytokine levels. Similarly, although day 1 coagulation abnormalities increased with illness severity and mortality, abnormalities also occurred in those subjects who never developed organ dysfunction and differences between the groups were modest.. Finally, the majority of inflammatory and coagulation markers peaked on day 1, indicating that these changes were already underway prior to presentation.

Numerous animal and human studies have been conducted to examine the effect of aging on the inflammatory and hemostasis response in sepsis. Older mice subjected to experimental sepsis, either by lipopolysaccharide (LPS) inoculation or by cecal ligation and puncture (CLP), have higher circulating inflammatory and hemostasis response and have higher mortality compared to younger mice [43-45]. While older mice tend to have an exaggerated inflammatory and hemostasis response to sepsis, the relationship between high systemic cytokine levels and mortality appears independent of age [46]. For example, at 24 hours following CLP, old mice have an approximately 7-fold increase in circulating TNF and IL-6 and a 2.5-fold increase in mortality compared to younger mice with equivalent CLP inoculum. However, when young mice receive an increased inoculum of CLP such that mortality between septic young and old mice are matched, they expressed an increased inflammatory profile similar to old mice [46].

Until recently, few studies examined whether the age-related differences seen in mouse models of sepsis were reflected in adults hospitalized with sepsis (Table 1). These studies were limited by either small sample sizes or by data collection at only one time point, thus limiting the ability to examine the trajectory of inflammation and coagulation response during the course of hospitalization. We recently sought to determine whether age related differences in inflammation and hemostasis response existed in a large cohort of adults hospitalized with pneumonia-induced sepsis [6]. Surprisingly, despite an age-related increase in risk of severe sepsis and mortality, there were no age related differences in inflammatory markers, including IL-6, TNF, and IL-10, during the first day of hospitalization or over the first

Table 1. Prospective observational cohort studies examining age-related differences in inflammation and/or hemostasis response in adults hospitalized with infection.

Author	Study design	Biomarkers	Sample Characteristics	Pertinent results	Interpretation
Kale, S., et al. (2010)	♦Patients hospitalized with CAP and admitted through the ED. ♦Biomarkers collected at enrollment, daily for the first week, and upon hospital discharge.	Pro-inflammatory: IL-6 and TNF Anti-inflammatory: IL-10 Hemostasis: D-dimer, TAT, AT-III, PAI-1, F-IX.	N=2183 <50yr, n=495 50-64yr, n=444 65-74yr, n=403 75-84yr, n=583 ≥85yr, n=258	No age-related difference in inflammatory markers at presentation and minimal pro-coagulant response in older adults. At discharge, there is a significant, but modest, age-related increase in IL-6 and a modest pro-coagulant response.	Minimal to modest age-related differences occur in inflammation and hemostatsis upon hospitalization for CAP. However, resolution of inflammation may be delayed in older adults at discharge.
Kelly, E., et al. (2009)	♦Patients hospitalized with CAP and admitted through the ED. ♦Biomarkers collected at enrollment.	Pro-inflammatory: IL-6 Anti-inflammatory: IL-10	N=80 <65yr, n=21 >85, n=59	Levels of IL-6 and IL-10 were similar between age groups.	Older age not associated with blunting of the inflammatory response.
Marik, P., et al. (2001)	♦Cohort of patients presenting to hospital with septic shock.‡ ♦Biomarkers collected on enrollment.	Pro-inflammatory: IL-6, TNF-α, sTNFR-75	N=930 <50yr, n=280 50-64yr, n=242 65-74yr, n=210 75-84yr, n=150 ≥85yr, n=48	TNF in oldest group significantly higher than in those 50-64yr and 75-84yr groups. Other markers were similar across age groups.	Older age not associated with diminished pro-inflammatory cytokines in subjects presenting with septic shock.
Bruunsgaard, H., et al. (1999)	♦22 consecutive patients hospitalized with *Streptococcus pneumoniae* infection. ♦Biomarkers collected on days 1, 3, 7 of hospital stay.	Pro-inflammatory: TNF-α, IL-β, IL-6 Anti-inflammatory: IL-10, sTNFR-1, IL-1RA Chemokine: MIP-1β	N=22 37-55yr, n=10 68-91yr, n=12	No age-related difference in cytokines on Day 1, but TNF-α and sTNFR-1 levels higher on Day 7 in elderly vs. young.	Older age associated with prolonged inflammatory activity following infection.

NF= tumor necrosis factor. sTNFR= soluble TNF receptor. IL=interleukin. MIP= macrophage inflammatory protein. TAT= thrombin-antithrombin complex. AT= antithrombin. PAI= plasminogen activator inhibitor. ‡Subjects analyzed were placebo arm of North American Sepsis Trial (NORASEPT II) study

week. While hemostasis markers revealed a pro-coagulant profile in older adults, the differences were modest and did not explain differences in outcome. Our findings of no age-related change in inflammatory profile are similar to results from two smaller studies [47, 48].

Our results suggest that, at least by the time of hospitalization, the dysregulated inflammatory and hemostasis host response that characterizes severe sepsis is quite similar across age groups. Furthermore, our results suggest that absolute levels of systemic inflammation and hemostasis do not alone explain worse outcomes. Although severe sepsis and mortality were associated with the highest levels of inflammation, older adults had higher levels of organ dysfunction even at less pronounced levels of inflammation.

How do we resolve the discrepant results of animal and human studies? First, animal studies measured cytokines during early sepsis, within 24-48 hours after exposure to infection, whereas human studies measure cytokines several days later after presentation to the emergency department. Whether early immune response differs among younger and older individuals is unknown. It is not practical to measure the immune response immediately after exposure to infection in clinical studies. Experimental models of sepsis, such as intravenous LPS, can measure cytokines over time under controlled conditions, but these studies are rarely performed in older adults due to safety reasons. Second, older adults have multiple chronic diseases and may have organ dysfunction prior to exposure to infection. Thus, the same inflammatory load may increase risk of organ dysfunction among older adults. Whether older animals have reduced organ reserve, similar to human studies, is not known.

Although clinical studies did not show large differences in inflammatory and coagulation markers between older and younger adults, these studies did not measure inflammation and hemostasis response at the tissue level, which could be age-dependent. Only selected markers were measured, and several important sepsis mediators, such as macrophage migration inhibitory factor (MIF), gamma interferon, and high mobility group box protein-1 (HMGB1), which have shown promising results in animal studies, were not measured [49-51].

Persistent inflammation and recovery

The traditional focus of care in patients with critical illness has been to reduce short-term and ICU mortality. However, the improved care of critically ill patients has improved short-term outcomes of sepsis. In recent years, interest in understanding the impact of infection on longer-term outcomes has increased [52, 53]. Studies examining long-term outcomes in older adults with serious infection suggest an increased risk of adverse events that persists well beyond hospital stay. In a study of more than 150,000 elderly Medicare recipients hospitalized with CAP, 1 in 3 patients who survived hospitalization for CAP died within the following year [54]. In a prospective cohort study of adults hospitalized with pneumonia, adults ≥ 85 years had a 1.3-fold and 2-fold increased risk of 1-year post-discharge mortality than those 75-84 years and 65-74 years, respectively [6]. Long-term mortality after sepsis, using data from the National Death Index, is most often due to cardiovascular disease, exacerbation of chronic obstructive lung disease, cancer, or repeat infection [55].

Adverse long-term outcomes are not limited to increased mortality risk. Several studies have also reported that survivors of critical illness develop physical and cognitive disabilities in the months and years after discharge [56, 57]. Recently, Iwashyna and colleagues analyzed data from an observational cohort of 1194 older adults to determine risk of cognitive impairment after all-cause sepsis [58]. During the 1-8-year follow-up, the risk of moderate-to-severe cognitive impairment increased 3-fold, from 6.1% before severe sepsis to 16.7% afterward. Extrapolating from national data, this would add approximately 20,000 new cases of moderate-to-severe cognitive impairment in the United States each year. Furthermore, severe sepsis was independently associated with the onset of 1.5 new physical limitations in patients who did not have a history of severe physical limitations.

Although observational studies cannot prove causation, these studies suggest that pathophysiological processes initiated during infection may lead to long-term consequences. In particular, recent studies suggest that the immune response activated during an acute infection may remain activated during recovery and is associated with higher long-term morbidity and mortality. We have recently shown that survivors of CAP have age-related increased circulating concentrations of IL-6 and hemostasis makers at hospital discharge, despite exhibiting normal vital signs and thus apparent clinical recovery [6]. Circulating markers were at least 4-fold higher than have been reported at baseline in community-dwelling individuals with similar ages, suggesting that dysregulated inflammation may persist at discharge. The higher concentrations of IL-6 at discharge were associated with increased risk of death over 3 months [59]. These studies suggest some survivors of critical illness may experience persistent inflammation. Similarly, we showed that the elevated levels of hemostasis observed during pneumonia hospitalization may persist at hospital discharge [60]. Higher levels of

D-dimer at discharge were associated with higher risk of death over 1 year. Persistent inflammation and hemostasis response may interact with and worsen chronic and subclinical conditions, such as cardiovascular disease. An important limitation of our work is that inflammatory and hemostasis markers were measured up to hospital discharge. The exact duration for which these markers remain upregulated after discharge remains unclear, and whether specific trajectories of inflammatory markers over time would be associated with long-term outcomes remains unknown.

There are several explanations for a persistent pro-inflammatory state following sepsis. First, resolution of inflammation is an active and highly regulated process that may be age-dependent [8, 61]. It is now appreciated that anti-inflammatory mechanisms are activated within the first few hours of acute inflammation [61]. Prostaglandin-derived lipoxins and resolvin D2 induce apoptosis in neutrophils and help stem the inflammatory response from sepsis [62]. These systems may be impaired with age. For example, aging is associated with diminished lipoxin levels [63]. If so, the profound inflammation and coagulation that occurs during sepsis may in fact persist at a lower level for months after apparent recovery. Additionally, patients with severe sepsis and acute respiratory distress syndrome have been found to have deficient glucocorticoid mediated down-regulation of inflammation, despite elevated levels of circulating cortisol [9, 10].

Second, sepsis may accelerate cellular senescence in older adults. Cellular senescence is triggered by a wide range of stimuli, including DNA damage and oxidative stress, both of which are hallmarks of sepsis. Although thought to be primarily an adaptive mechanism that stops cancer progression in vivo though irreversible cellular arrest, cellular senescence from fibroblasts and epithelial cells are associated with secretion of several pro-inflammatory molecules, such as IL-6, IL-8, and IL-1 [22]. This unintentional deleterious effect is proposed to be a contributor to the chronic inflammatory state of aging, and may be further exacerbated after critical illness. Further studies will be needed to examine the persistence of elevated inflammatory markers in the months following hospitalization.

Conceptual model and interventions

Based on our interpretation of the current literature, we have developed a conceptual model of age-related inflammatory and hemostasis abnormalities prior to, during, and after sepsis (Figure 2). As our model demonstrates, the aging process is associated with a baseline increase in inflammation and hemostasis abnormalities (dark black line). In our model, three potential outcomes are possible during hospitalization for severe sepsis and critical illness. In younger age, critical illness is associated with a sharp increase in inflammation and hemostasis response and a quick resolution (Curve A). In older age, severe sepsis results nearly 25% short-term mortality (Curve B). Even in older survivors of critical illness, however, the inflammation/hemostasis abnormalities associated with critical illness fail to fully resolve, placing them on a new trajectory (Curve C). This new trajectory is associated with a higher risk of repeat critical illness and increases the risk of subsequent death. At each stage of the continuum, specific interventions in the elderly to decrease inflammation and hemostasis abnormalities may decrease risk of sepsis and mortality.

A review of current treatments for sepsis is beyond the scope of this manuscript; however recent studies attempting to modulate the early inflammation and hemostasis response during sepsis have shown some success. Recombinant activated protein C (rhAPC), known to alter the coagulation cascade, was approved by the US Food and Drug Administration for use in patients with sepsis-induced organ dysfunction. The PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) trial demonstrated a 61% absolute decrease in mortality (30.8% vs. 24.7%, p=0.005) in patients with severe sepsis [64]. Results of randomized clinical trials to assess efficacy of low-moderate dose glucocorticoids have shown conflicting results [65, 66]. Additionally, the efficacy of statins have been examined in observational studies and small clinical trials due to their pleiotropic effects on inflammation, endothelial dysfunction, and oxidative stress pathways [67-69]. A meta-analysis of existing observational studies showed that statins were associated with a reduction in the development of infection in high-risk patients as well as improved outcomes in patients admitted with infections [69].

Studies to date that test immunomodulatory therapies have focused on modulating the early immune response and these therapies have been used for short duration, often limited to ICU stay or during the first week of hospitalization. Whether extending these treatment strategies up to or beyond hospital discharge can improve long-term outcomes remains unknown. Trials are underway to test interventions for longer duration, such as glucocorticoid therapy for 20 days in patients with severe community-acquired pneumonia [70]. In particular, therapies employed for a longer duration may be beneficial in older adults who have higher burden of chronic disease prior to onset of severe sepsis and may be at higher risk for a dysregulated immune response.

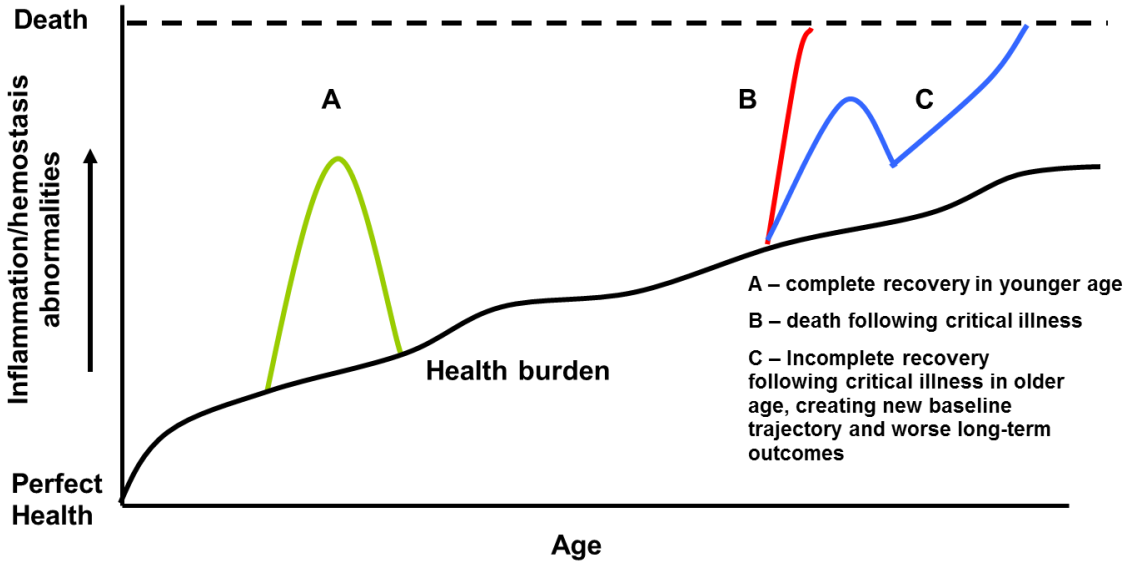

Figure 2. Conceptual model showing the relationship between inflammation/hemostasis abnormalities throughout the continuum of critical illness and aging. Aging is associated with a baseline increase in inflammation and hemostasis abnormalities (dark black line). Three potential outcomes are shown following sepsis. Younger adults have a lower incidence and mortality with and are expected to return to baseline inflammatory and hemostasis levels after infection (A). In older adults, a higher baseline inflammation/hemostasis burden increases the risk of sepsis and higher mortality (B). Even among older survivors of sepsis, processes that down-regulate inflammation after infection may be dysregulated, leading to a higher inflammation/hemostasis burden post-infection and worse long-term outcomes, including repeat infection and exacerbation of chronic conditions (C).

Conclusion

Older age has long been associated with altered inflammation and hemostasis regulation, which has been linked to the development of chronic diseases. Emerging evidence suggests that age-related differences in inflammation and hemostasis abnormalities may play a role in the development of and long-term outcomes after critical illness. A better understanding of underlying mechanisms may provide new possibilities for therapeutic interventions.

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