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Divergent Sepsis Pathophysiology in Older Adults

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Abstract

Significance: Both incidence and mortality rates of sepsis significantly increase with advanced age, and the majority of sepsis patients are late middle-aged or older. With the proportion of older adults rapidly increasing in developed countries, age-dependent sepsis vulnerability is an urgent medical issue. Due to an increasing life expectancy, postsepsis complications and health care costs are expected to increase as well.
Recent Advances: Older patients suffer from higher sepsis incidence and mortality rates, likely resulting from frequent comorbidities, increased coagulation, dysgylcemia, and altered immune responses.
Critical Issues: Despite a large number of ongoing clinical and basic research studies, there is currently no effective therapeutic strategy targeting older patients with severe sepsis. The disparity between clinical and basic studies is a problem, and this is largely due to the use of animal models lacking clinical relevance. Although the majority of sepsis cases occur in older adults, most laboratory animals used for sepsis research are very young. Further, despite the wide use of combination fluid and antibiotic treatment in intensive care unit (ICU) patients, most animal research does not include such treatment.
Future Directions: Because sepsis is a systemic disease with multiple organ dysfunction, combined therapy approaches, not those targeting single pathways or single organs, are essential. As for preclinical research, it is critical to confirm new findings using aged animal models with clinically relevant ICU-like medical treatments. *Antioxid. Redox Signal.* 35, 1358–1375.

Keywords: sepsis, aging, comorbidity, inflammation, thrombosis, oxidative stress

Introduction

Sepsis is a life-threatening illness that results from infection. Despite advancing medicine, sepsis remains a serious global health issue, with an annual estimated 48.9 million cases and 11.0 million deaths worldwide (138). In the United States alone, annual incidence rates range from 15% to 20% with mortality rates upward of 30%, making sepsis the most expensive condition treated in U.S. hospitals (68, 99, 167). Similar trends are observed in other developed countries such as Japan, Australia, China, Canada, and Germany (4, 138). Figure 1 shows the increase in sepsis-related hospitalizations compared with total hospital costs over the past decade. Annual estimates range from $23.7 to $62 billion, and those numbers are only expected to rise with increased life expectancies and a growing aging population (138).

Sepsis is particularly devastating to older adults, with 58%–65% of sepsis cases presenting in those ≥65 years of age (13, 41, 105). It is estimated that 1 in 9 adults will be older than 65 by 2030 and the global aged population will double by 2050 (173a). Thus, advancements in sepsis research and clinical care targeting older adults are critical. In this article, we will review our current understanding of sepsis pathophysiology characteristics of older adults (*i.e.*, ≥65 years of age) and the biological mechanisms that likely contribute to their higher incidence and mortality rates.

Sepsis Pathophysiology Characteristics of Older Adults

Increased incidence and mortality

Sepsis incidence has been steadily increasing over the past several decades. Hajj *et al.* reported an incidence of 82 per 100,000 individuals in 1979, which increased to 436 per 100,000 in 2012 (65). Current estimates for 2017 are 677.5 per 100,000 (138). Sepsis is especially prevalent in older patients, with incidence rates nearly 100-fold higher as

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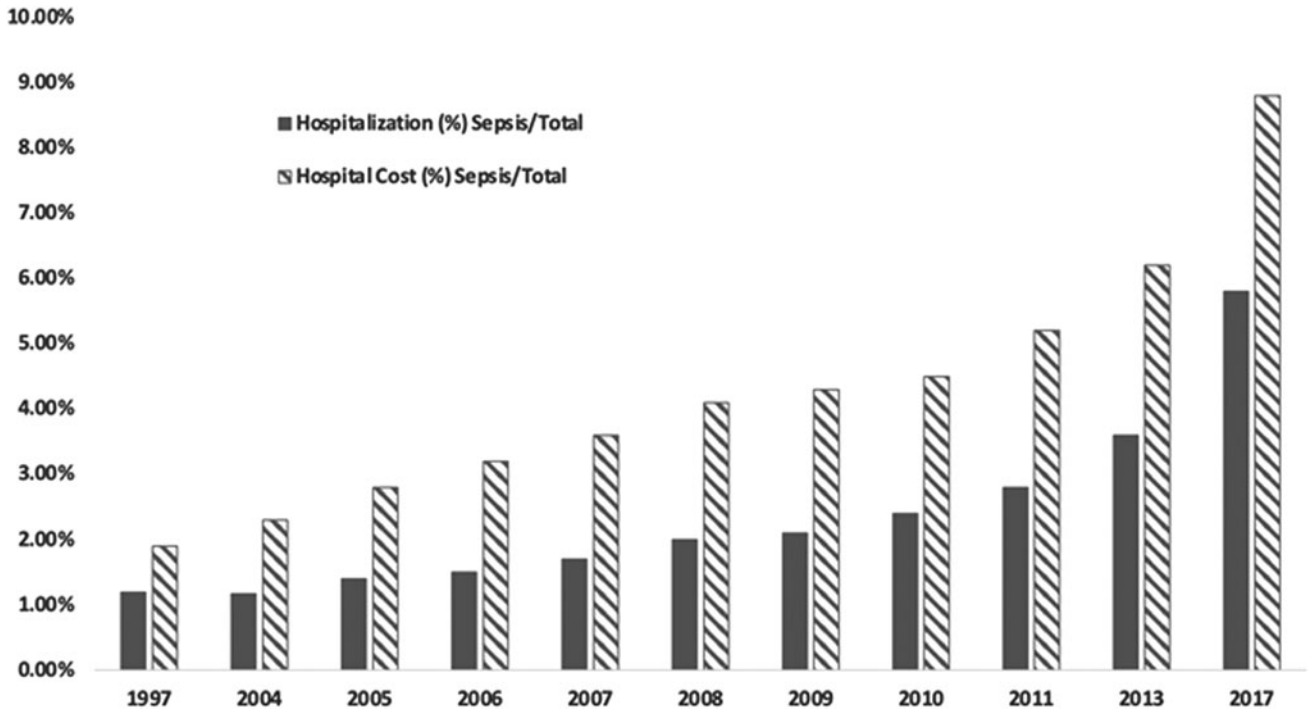

FIG. 1. The percentage of sepsis hospitalizations and costs has risen significantly over the past 20 years. Hospital costs related to sepsis have risen from 1.9% of total U.S. hospital costs in 1997 to 8.8% of total hospital costs in 2017. Once adjusted for 2020 inflation, this translated to an increase from $5 billion in 1997 to $41 billion in 2017. The percentage of sepsis-related hospitalizations has risen from 1.2% to 5.8% of total hospitalizations over the same 20-year period. The data for 2012 and 2014–2016 were unavailable. A graph is generated from the summarized data from HCUP Statistical Briefs (11, 12, 44, 99, 138, 165, 166, 181, 182).

determined by Angus *et al.* (0.2/1000 in children, 5.3/1000 in those aged 60–64, and 26.2/1000 in patients ≥85) (13, 14). Martin *et al.* found that over a 24-year period (1979–2002), growth rates of sepsis incidence were 20.4% higher for those ≥age 65; those <age 65 showed a mean increase of 9.5% per year over the 24 years; and those 65 and older had an annual incidence increase of 11.5% (105).

Older patients also have markedly increased sepsis mortality rates. A set of early studies concluded that older patients have mortality rates of 30%–40% whereas younger patients have rates of 4%–5% (152, 162). More recently, Kotfis *et al.* reported that sepsis patients age 50 and younger have an in-hospital mortality rate of 25.2%, whereas those aged 61–70 have a rate of 33.1%, and those older than 80 years have an even higher in-hospital mortality rate of 49.3% (89). Nasa *et al.* found that in severe sepsis/septic shock, those older than 80 had mortality rates of 78.9% whereas those younger than 60 had a mortality rate of 45.6% (113). Older patients suffer from gram-negative bacterial sources of infection at higher rates than younger individuals (38, 58, 99, 105, 113). This may be attributed to multimorbidity, increased rates of prior surgical intervention and catheter use among older patients, age-associated immunosenescence, and overall increased antibiotic resistance (58, 107, 113).

The burden of sepsis lasts long after an individual is discharged from the hospital, as sepsis survivors often suffer from prolonged fatigue, mental health issues, cognitive impairment, an altered immune system, and even death (37, 40, 130). After sepsis, nearly one-third of sepsis survivors are discharged to assisted living facilities, and this is associated with higher 1-year mortality rates (43). Indeed, older patients are more frequently discharged to assisted living facilities, underscoring the more severe course of sepsis in older patients (113). In the time after hospital discharge, those who were admitted for sepsis have higher 30-day to 3-year mortality rates when compared with nonsepsis-related hospitalizations, with advanced age having even higher mortality rates at the 1-year mark (26, 68, 113). Buchman *et al.* reported that those patients aged 65–74, 75–84, and 85+ are predicted to have 1.36, 1.92, and 3.38 higher odds of death 1 week after discharge and 1.66, 2.68, and 5.77 higher odds of death at the 1-year mark, respectably, as compared with those younger than 65 years of age (26).

Generally, aging is associated with a reduction of stress tolerance (Fig. 2A). An age-associated increase in mortality rates has been confirmed by studies using animal models of sepsis and systemic inflammation. Earlier studies, with sterile systemic inflammation models using bacterial endotoxin or lipopolysaccharides (LPS), reported significantly increased mortality rates in aged mice as compared with younger mice or rats (35, 63, 140). These findings were later confirmed by abdominal sepsis models, including the cecal ligation and puncture (CLP) surgical model and the cecal slurry injection model (Fig. 2B) (157, 172). Besides increased mortality, aged animals exhibit increased inflammatory cytokine production and enhanced coagulation, indicating severe systemic inflammation (Fig. 2C, D).

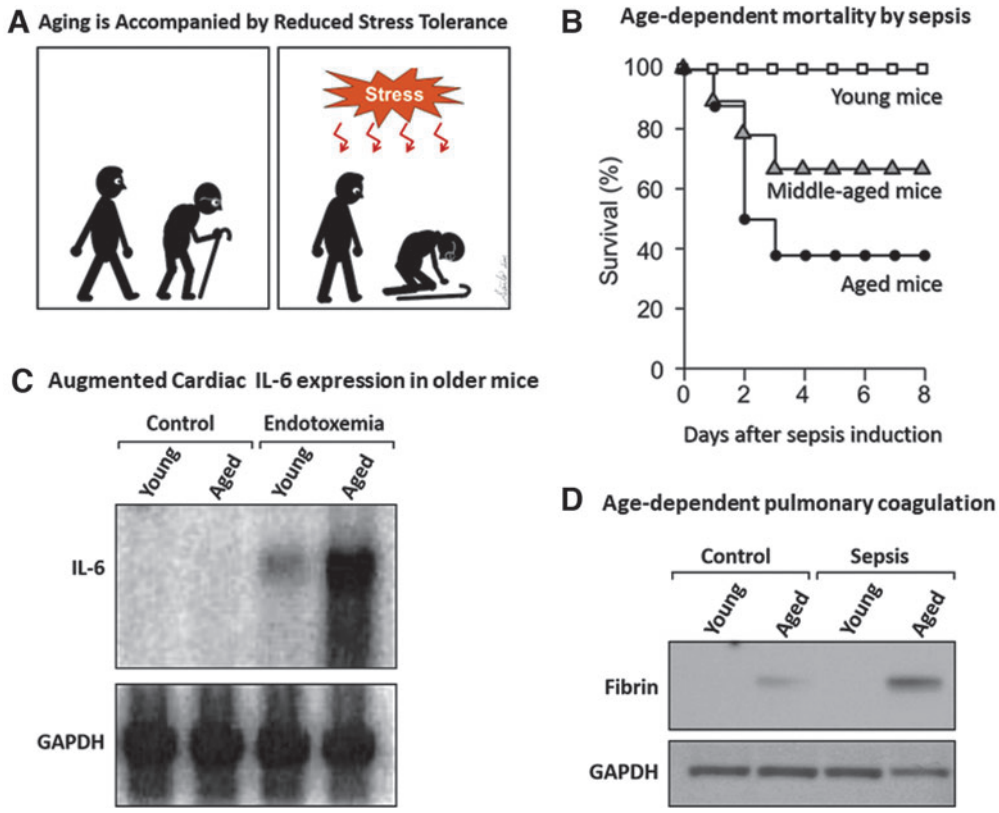

FIG. 2. Age-associated vulnerability to stress. (A) Aging is associated with reduced physiological stress tolerance. Older adults develop more exaggerated responses to mild infection, injury, surgery, or trauma whereas younger individuals do not. **(B)** A survival test demonstrating age-dependent mortality by sepsis. Survival after cecal slurry-induced abdominal sepsis was monitored in young adult (4- to 6-month-old, $n=7$), middle-aged (12- to 14-month-old, $n=9$) and aged (24–26 months old, $n=8$) male C57BL/6 mice. [Adapted from Starr *et al.* (157).] **(C)** Northern blot analysis demonstrating age-dependent overexpression of cardiac IL-6 mRNA 6 h after induction of endotoxemia. Young adult (4 months old) and aged (24 months old) male Blab/c mice were injected intraperitoneally with LPS (~ 1.5 mg/kg body weight, $n=4$ pooled in each group.) [Adapted from Saito *et al.* (140).] **(D)** Western blot analysis demonstrating age-dependent increase in fibrin formation (*i.e.*, blood clot) 24 h after sepsis induction. Abdominal sepsis was induced in young adult (4–6 months old) and aged (24–25 months old) male C57BL/6 mice by cecal ligation and puncture, and whole lung was collected for fibrin analysis ($n=4$–5 in each group). [Adapted from Starr *et al.* (158).] LPS, lipopolysaccharide.

Absence of fever

A common manifestation of sepsis is the development of fever. However, as older adults tend to have lower body temperatures, fever (oral temperature ≥37.8°C [100°F] or rectal temp ≥37.5°C [99.5°F]) is absent in older sepsis patients up to 50% of the time, making diagnosis more difficult (137). In addition, hypothermia (<36.0°C [96.8°F]), which also occurs during sepsis, is more common in older patients and is associated with higher sepsis mortality rates (165). The development of hypothermia after sepsis is confirmed by our several preclinical studies with murine models; although sepsis- and endotoxemia-induced hypothermia is common in both young and aged mice, these studies found that hypothermia is more profound in older animals and is highly associated with increased systemic inflammatory cytokine production and mortality (141, 158).

Dysglycemia

Sepsis often causes abnormalities in blood glucose levels (*i.e.*, dysglycemia). Both hyperglycemia and hypoglycemia occur with sepsis and can contribute to in-hospital and postdischarge mortality (9, 32, 33, 54, 117). An early study by Kagansky *et al.* found that aged (≥70 years) hypoglycemic patients had double the in-hospital and 3-month mortality rates, despite hypoglycemia not being an independent predictor of mortality (81). Higher mortality rates for hypoglycemic sepsis patients were confirmed by another study also showing that longer inpatient stays are associated with low blood sugar (54, 129).

During sepsis, hypoglycemia is often a result of intensive insulin therapy to avoid hyperglycemia. Nugent *et al.* reported that mild and severe hyperglycemia in sepsis patients correlated with older age, and those with severe hyperglycemia suffered higher 30-day mortality rates regardless of diabetic state (117). However, there is emerging evidence that mild hyperglycemia may be beneficial, and intensive insulin therapy should be avoided (62, 143, 164). Noting that closely maintained glycemic control protocols do not appear to improve mortality, Marik and Bellomo suggested that hyperglycemia is an adaptive response to promote survival (104). Green *et al.* found that hyperglycemia alone did not impact mortality rates in nondiabetic patients

admitted to the hospital for sepsis (62). In fact, Tiruvoipati *et al.*'s study found stress hyperglycemia to be associated with lower intensive care unit (ICU) mortality rates in septic shock (164).

Coagulation

Disseminated intravascular coagulation (DIC), resulting from inflammation-driven microvascular endothelial cell damage and vascular leakage, is a particularly deadly complication in sepsis. Not only does inflammation drive coagulation, but also increased coagulation further perpetuates inflammation resulting in a positive feedback loop (96). Hypotension, compromised blood circulation, tissue ischemia, and organ failure are all downstream consequences of increased coagulation. The DIC also commonly results in coagulopathy (bleeding) once platelets and coagulation factors are exhausted (75, 78). Kelm *et al.* reported that DIC development in sepsis led to higher mortality rates when compared with sepsis controls without DIC (68% instead of 38%) (85). Lyons *et al.* found that as the severity of sepsis-associated coagulopathy increased, the duration of hospitalization and requirement for ICU care did in tandem (102). This study also found an association between increased mortality and coagulopathy (102). ''Sepsis-induced coagulopathy'' that can progress to DIC was recently introduced to better describe and diagnose the fibrinolytic phenotype of coagulopathy in sepsis (75, 76). However, its relation to aging has yet to be characterized.

Enhanced thrombosis in the aged has been demonstrated in preclinical models of sepsis. We have shown that age-dependent fibrin formation in the lung and kidney using murine models of LPS-endotoxemia, CLP-abdominal sepsis, and acute pancreatitis is an inflammatory disease that often progresses to sepsis (Fig. 2D) (119, 158, 159). In two of our previous studies in which the sepsis or endotoxemia mortality rate was titrated to be equivalent in young and aged mice, only aged mice showed significant fibrin formation, indicating that enhanced coagulation is due to advanced age, not the age-dependent severity of sepsis (158, 159). This is in contrast to cytokine production; IL-6 production in young and aged mice is equivalent when sepsis severity is similar between the groups (159).

It is noteworthy that young mice hardly show fibrin formation although thrombotic biomarkers such as d-dimer and plasminogen activator inhibitor 1 (PAI-1) are elevated, highlighting that the use of appropriately aged animals for studying sepsis-induced coagulopathy is critical.

Comorbidities

Comorbidities typically develop with advancing age, and their role in sepsis should not be overlooked. Figure 3 outlines several factors that contribute to the increased rate of sepsis incidence and mortality in older individuals. Comorbidities and multimorbidities emerge increasingly starting at age 50, and several of these are negatively associated with both the initial survival of sepsis and survival in the months after sepsis (188, 48). This suggests that comorbidities are a factor not only in sepsis development and survival but also in long-term quality of life after sepsis recovery.

Cancer

Cancer-related sepsis has an 8.4% higher mortality rate than noncancer-related sepsis, and 9% of all cancer-related deaths are due to sepsis (5, 68). Sepsis patients with cancer make up 12% of total sepsis admissions in the United States, and malignancy serves as the most common sepsis comorbidity (50, 68). In a retrospective study of sepsis patients in Lebanon, the mean age of septic patients with cancer (65.39 ± 15.04 years) was lower than the noncancerous sepsis control group (74.68 ± 14.04 years), indicating that cancer predisposes patients to earlier bouts of sepsis (5). The increased incidence and mortality rates of cancer-related sepsis are typically associated with the immunosuppressive effects of chemotherapy. Indeed, Li *et al.* found that 18.8% of cancer patients developed infections requiring hospitalization after their first round of chemotherapy (98).

Murine models have revealed that cancer, without chemotherapy treatment, also leads to worsened mortality rates. Allen *et al.* recently published that cancer itself can decrease the body's ability to fight infections, as T cell dysfunction accompanies malignancies (10). Fox *et al.* looked at the interaction between sepsis and cancer and found that septic mice with cancer had higher rates of B and T cell apoptosis (50). Taken together, cancer itself can elevate the risk of sepsis incidence and mortality, whereas chemotherapy treatment further increases both.

Diabetes mellitus

Diabetes is a major comorbidity of sepsis, comprising 20%–23% of sepsis patients (4, 88). Indeed, both type 1 (T1DM) and 2 (T2DM) diabetes increase sepsis incidence and mortality (29, 53, 74, 88, 129, 144, 168, 190). Hsieh *et al.* found that sepsis patients with T2DM have higher in-hospital and 28-day mortality rates when compared with nondiabetic sepsis controls (74). Both T1DM and T2DM cause a decreased innate immune response, thus increasing the risk of general infections and sepsis in terms of both incidence and mortality (29, 57, 129, 168, 190). Neutrophil function, including decreased adhesion and migration, is especially common in T1DM and leads to a reduced ability to clear and regulate sepsis-causing infections (6, 27, 168). In T2DM, higher mortality rates may be driven by heightened insulin resistance and inflammation (21, 168).

Animal models of sepsis in rats with T1DM and T2DM revealed 75% and 30% higher mortality rates, respectively (168). Schuetz *et al.* reported higher mortality rates in diabetic mice, crediting decreased bacterial clearance as a major reason for the increase (144).

Dementia

A study by Shen *et al.* found that dementia increases severe sepsis incidence by 50%, in-hospital mortality risk by 28%, and also increases the risk of acute organ dysfunction in sepsis patients by 32% (148). Bouza *et al*. reported that dementia raises mortality rates in individuals aged 65–69 as well as individuals ≥90 years of age, despite a greater degree of comorbidities in the older age group (25). However, the same study also reported that patients with sepsis and dementia had paradoxically lower rates of organ dysfunction and shorter hospital stays than nondementia sepsis patients

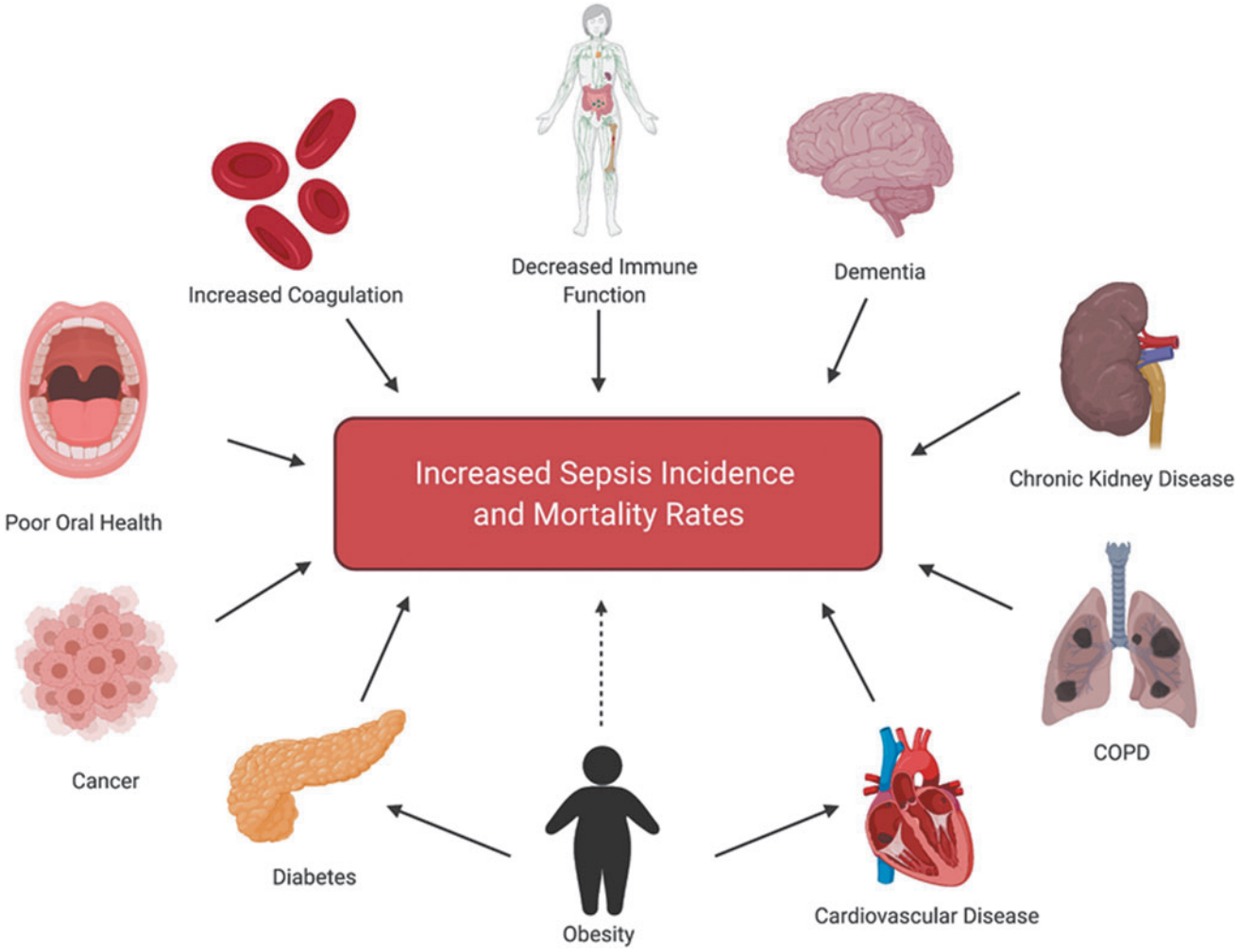

FIG. 3. Age-associated multiple comorbidities and other factors that contribute to increased sepsis incidence and mortality rates. Shown by the solid *arrows*, decreased immune function (73), cancer (50, 68), COPD (34, 90, 95, 109, 145), chronic kidney disease (69), dementia (25, 37, 147), increased rates of coagulation (64, 183), poor oral/dental health (80, 132, 146), cardiovascular disease (94), and diabetes (27, 88, 167) all increase sepsis risk and mortality. Further, obesity serves as a comorbidity and risk factor for several conditions, notably diabetes and cardiovascular disease. Although obesity's role in sepsis is still unclear, it may have a negative impact on incidence and mortality rates in older adults (*dashed line*) (3, 107, 122, 186). All of these conditions occur more frequently with age, thus contributing to higher rates of sepsis incidence and mortality in older populations (≥65 years old) (186a, 48). COPD, chronic obstructive pulmonary disease. Figure created with BioRender.com

(25). These disparities need to be clarified in future studies. Sepsis itself induces long-term cognitive impairment in more than 50% of sepsis survivors, with some cases warranting a mild Alzheimer's disease diagnosis (37). Preexisting cognitive deficits and neurological disorders have been deemed a risk factor for developing sepsis-associated encephalopathy, further suggesting that dementia could have a negative impact on both sepsis survival and quality of life after sepsis (37).

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease that starts at or after middle age and elevates the risk of chronic and acute respiratory tract infections (95, 146). Pulmonary infection, including pneumonia, is a leading cause of sepsis. A study by Montull *et al.* determined COPD to be a risk factor for severe sepsis brought on by pneumonia (110). The study found that 37.6% of those hospitalized for community-acquired pneumonia had already developed severe sepsis on hospital admission, confirming that the two are closely linked (110). Kukrety *et al.* concluded that accelerated aging leads to COPD, noting that several hallmarks of aging such as telomere shortening and cellular senescence are seen in COPD pathogenesis (90). A Taiwanese study by Chen *et al.* sorted COPD patients into sepsis and nonsepsis groups and found that the sepsis survivors with COPD had higher in-hospital to 2-year mortality rates than the nonsepsis COPD individuals (34).

Obesity

Obesity, though not unique to older adults, is among the most common and costly comorbidities, representing more than 20% of total annual medical spending in the United

States (30). Although obesity increases the risk of developing poor health conditions such as diabetes, cardiovascular disease, and some cancers, epidemiological studies have reported that being overweight or obese confers a survival advantage during sepsis (30, 84, 97, 125, 126, 177, 179). This emerging phenomenon is referred to as the ''obesity paradox'' (84, 115, 136).

With respect to aging, current data are inconclusive as to whether age plays a role in the obesity paradox. In their recent retrospective analyses of 55,038 adult sepsis patients, Pepper *et al.* conducted subgroup analyses for age (<65 or ≥65) and found that overweight and obese patients (class I–III) had lower short-term mortality (in-hospital or discharge to hospice) than normal-weight patients, regardless of age group (125). However, Abbate *et al.* found that the association between obesity and sepsis survival was modified by age in that obesity was associated with lower mortality in older adults (>50 years) but not younger adults (<50 years) (3). Although the association between obesity and increased survival is reflected in numerous clinical studies, a few studies were inconclusive or found no association after adjusting for age or other comorbidities (15, 56, 92, 123).

Further complicating the validity of this phenomenon is the fact that preclinical studies have mostly been unable to confirm the obesity paradox using sepsis models with dietary-induced obese animals (108, 187). Some preclinical studies reported that diet-induced obesity increased survival after CLP-induced sepsis (151, 170), whereas others found no effect (122), or showed reduced survival in obese mice (83). This discrepancy may well be due to different experimental designs, including the age of animals used and the degree of metabolic syndrome influenced by a varied duration of high-fat diet feeding. Many studies using LPS, single-strain bacteria, or single-strain viruses failed to reproduce the obesity paradox showing either no effects of obesity on survival or reduced survival in the obese (187).

Though questions surrounding the ability of obesity to promote survival during sepsis remain, it is known that visceral adipose tissues (VAT) have pathological roles in sepsis as both clinical and preclinical studies found that VAT is a major source of several pro-inflammatory cytokines (*e.g.*, IL-6) and pro-thrombotic mediators (*e.g.*, PAI-1) (153, 154, 194). Short-term dietary restriction has also been shown to significantly reduce body weight, the amount of VAT, and result in increased survival of middle-aged mice under both sepsis and endotoxemia models (156). Thus, a balance between the negative pathological role of visceral fat and the potential protective effects of the obese state must exist if obesity is deemed protective in sepsis.

Dental and periodontal diseases

Recently, it is increasingly recognized that poor oral health negatively affects older adults' general health (42). Ondontogenic infections—those of the tooth or surrounding areas—can lead to sepsis as described by Jevon *et al.* (80). Older adults are more prone to ondontogenic infections as they undergo thinning of the oral mucous membrane, which is a critical barrier in pathogen protection (133). Oropharyngeal gram-negative rods are common in cases of nursing home-acquired pneumonia, suggesting that poor dental health has a role in nosocomial pneumonia development (147). Indeed, community-acquired pneumonia is responsible for a significant number of sepsis cases (31), indicating the importance of further investigation focusing on the link between ondotogenic infections, dental hygiene, and sepsis in older adults.

Other comorbidities

Various other comorbidities exist, and a few studies have attempted to highlight a link between them and sepsis incidence/mortality; however, the data are sparse. Chronic kidney disease can be classified as both a source of chronic inflammation and an immunodeficient state with decreased innate and adaptive immune responses, thus leading to a higher risk of developing sepsis (69).

Reports of cardiovascular disease developing after sepsis are also emerging, with heart failure and atherosclerosis commonly developing in the years after treatment for sepsis (94). Lai *et al.* found that those who are recovering from sepsis have a 4.48-fold increased risk of developing acute coronary heart disease in the first year after sepsis, with a 1.18-fold risk at the 4-year mark (94). Interestingly, younger sepsis survivors, those aged 20–45 years, had a higher absolute risk of myocardial infarction and stroke than those ≥75 years (94).

Biological Mechanisms for Increased Severity of Sepsis in Older Adults

Altered immune function

It is well established that immune system function declines with age. Age-associated low-grade chronic inflammation, or inflammaging, may underlie the exaggerated inflammation and subsequent immunosuppression observed in sepsis (51, 91, 191). Sepsis itself alters immune function, exacerbating the deleterious changes that occur with aging (7, 40, 73, 113). Nearly two-thirds of sepsis survivors develop chronic immunosuppression and inflammation, now termed PICS (persistent inflammation/immunosuppression and catabolism syndrome), which leaves them vulnerable to secondary infections, accounting for roughly 65% of total sepsis-related deaths (72, 106, 127). Platelet, T cell, B cell, neutrophil, natural killer (NK) cell, macrophage, and toll-like receptor (TLR) dysfunction all lend themselves to worsened sepsis outcomes (7, 36, 40, 55, 71, 145). Age- and sepsis-associated alterations of specific immune cell types are briefly discussed here.

Myeloid cells

Monocytes serve as precursors for macrophages and dendritic cells (145). Total monocyte counts do not change with age, but the proportion of monocytes in each subtype (classical, nonclassical, and intermediate) is reportedly altered (36, 55, 71). Namely, nonclassical monocytes increase with age; however, Seidler *et al.* suggest that increased number does not mean increased function, as migration and monocyte-derived macrophage half-life times are likely negatively impacted by aging (145). With sepsis, all three monocyte subclasses typically undergo expansion, and high total monocyte levels are linked to reduced bacteremia and better outcomes (36, 55, 71). Clinical data indicate that monocyte counts decreased with sepsis progression in non-survivors, whereas survivors saw increases (36). Further, low

levels, specifically of nonclassical monocytes (proinflammatory subtype with high TLR expression), are associated with worse outcomes (55).

Macrophages, classically divided into M1 (pro-inflammatory) and M2 (anti-inflammatory), play an important role in sepsis (101, 112, 118, 128, 150, 181). M2 macrophages aid in inflammation resolution and wound healing, whereas M1 macrophages produce pro-inflammatory cytokines and reactive oxygen species (ROS) to carry out their phagocytic and bactericidal functions (17, 103, 112, 118, 150). With aging, the ability of macrophages to mount an effective pro-inflammatory response is diminished (103). For example, macrophage-derived IL-1β and TNF-α levels are reduced by 25% compared with young mice (128). Concurrently, sepsis-induced apoptosis depletes macrophages, limiting their pathogen clearing abilities and eventually immunosuppression and secondary infection (28).

Neutrophils play a major role in phagocytosis, and decreased neutrophil migration and phagocytosis are linked to worse sepsis prognoses (36, 71, 192). Shen *et al.* noted that neutrophils can aggregate in the vasculature, promoting organ dysfunction during sepsis (149). Visan stated that with aging, neutrophils form extracellular traps, produce more ROS, and promote adhesion (176). Tsukamoto and Machida found that men older than 60 years old demonstrated decreased neutrophil function and correlated stressful events with age and lower rates of phagocytosis (171).

Platelets play critical roles in inflammation and hemostasis by interacting with other immune cells and promoting endothelial adhesion and extravasation of leukocytes at sites of inflammation. Platelet counts decrease by about 10% after age 70, and this is further depressed in sepsis (70, 109). Low platelet counts in sepsis have been associated with the development of DIC, although this trend is apparent only for the severely ill (16). Despite decreased platelet counts, platelet activity increases in both aging and sepsis, causing an exaggerated inflammatory response (16, 109). During sepsis, platelets can spontaneously aggregate, elevating the risk of arterial occlusions and coronary events (16, 169). Since older individuals already have increased coagulation, this is particularly dangerous in aged sepsis patients (64).

Lymphocytes

Lymphocytes include three main subclasses: T cells, B cells, and NK cells. Aging introduces changes to all three subclasses, which likely contribute to increased sepsis incidence and mortality in older adults (52, 59, 73, 111). Although the absolute number of T cells remains the same with age, the balance between naive and memory T cells shifts to favor memory cells (19, 59). This is problematic, because the ability of the remaining naive T cells to replicate in response to pathogen stimulation is suppressed (59). Further, T cells also lose their ability to recognize a diverse range of antigens with age, giving rise to decreased immunity (19). In sepsis, T cell exhaustion and persistent inflammation increase mortality rates, especially in older adults (77). Functional unresponsiveness and replicative senescence characterize T cell exhaustion, which ultimately results in an inability to activate macrophages and eliminate pathogens (77). T cell apoptosis also occurs during sepsis, driving immunosuppression (73).

Among the four B cell subsets (naive, IgM memory, late memory, and switched memory), late memory B cell proportions increase with age, and their higher proportions in blood are associated with poor vaccine response in the aged (52). This is pertinent to sepsis as vaccines are recommended to help prevent the progression of infection to sepsis, especially in older adults (22). Sepsis has also been shown to decrease antigen-specific antibody production in B cells, which leads to worse outcomes and diminished response to vaccines (38, 73). In sepsis, B cells also demonstrate exhaustion (120). This decreases the immune response as the ability of B cells to produce cytokines, secrete immunoglobulins, and activate T cells decreases (120).

NK cells are vital to the immune response, as decreased NK cell activity is associated with increased infection incidence (111). NK cells function declines with age as their ability to secrete cytokines and defend against pathogens decreases (52, 111).

The overall dysregulation of lymphocytes during sepsis may also inhibit the cross-talk between the innate and adaptive immune systems, further increasing the difficulty for the body to clear the infection (120). Combined with the impacts of aging, the sepsis-induced alterations to lymphocytes doubtlessly contribute to future infection incidence and increased mortality after discharge.

Toll-like receptors

Though not immune cells themselves, TLRs are critical in the immune response. TLRs are a class of pattern recognition receptors that have roles in detecting pathogens, regulating cytokine production, recognizing self and nonself antigens, and linking together the innate and adaptive immune system (116). Signaling downstream of TLRs is impaired in aging, as TLR2 and TLR4 become unable to mount proper cytokine responses (18). Indeed, whole blood treated with LPS *ex vivo* demonstrated decreased responses with increased age (18). This is likely a result of lower levels of CD80, decreased ERK phosphorylation, and/or chronic inflammation that causes an upregulation of TLR inhibiting deubiquitinases (18). Due to the critical role of TLRs in pathogen detection, their suppressed function in aging may contribute to a higher incidence of infection in older individuals. Acknowledging that TLRs play a central role in the development of sepsis, several therapies are attempting to target TLR4 (93, 142, 187).

Wound healing

Wound healing is an important component of the immune response, as it resolves tissue injury and prevents future infection (60, 61, 128, 131). The four overlapping stages of the wound healing process—hemostasis, inflammation, proliferation, and remodeling—require coordinated action by various types of cells, including macrophages, keratinocytes, endothelial cells, neutrophils, platelets, and fibroblasts (46, 61, 86, 87, 128, 134). Aging impacts each stage of the wound-healing response, which is delayed 20%–60% in aged animals (60, 131). Macrophage and neutrophil infiltration progress more slowly with advanced age, thus delaying healing (46). Keratinocyte migration slows as much as 50% in aged animals (60). Wound closure slows in older animal models as a function of decreased proliferation and production of fibroblasts, vascular endothelial cells, and keratinocytes (23, 60).

Older adults are more susceptible to infection as a result of these changes (23, 60). These age-related changes in wound healing are linked to an increased population of senescent cells, or cells displaying a senescence-associated secretory phenotype (180, 185). After sepsis in a murine model, wound-healing abilities are diminished compared with non-sepsis controls (39). In their review, Thornton *et al.* noted that sepsis may increase collagenolysis and that collagen synthetic capacity is decreased significantly in abdominal sepsis, diminishing strength in wound healing (163). Sepsis-induced immunosuppression may be furthered when wound fluid that depresses lymphocyte function in sepsis spills into the systemic circulation (163). Sepsis can also decrease the response of the cell types involved in wound healing, namely monocytes, macrophages, neutrophils, and platelets (7, 16, 40).

Coagulation

Although advancing age alone is associated with heightened coagulation, the propensity for this chronic condition to worsen DIC during sepsis is unknown (82, 184). Further, although the tendency to develop DIC is well characterized in sepsis, little is known about age-associated differences in the expression of thrombotic factors and how these relate to clinical outcomes (78, 82, 96). Although data are lacking on age-related differences in prothrombotic factors, clinical trials with activated protein C (aPC; Xigris) in severe sepsis showed that efficacy was greatest in elderly patients, suggesting heightened thrombosis in old age (8, 45).

Several preclinical studies address the mechanisms for age-dependent coagulation during sepsis or related systemic inflammatory conditions. An early study reported that induction of PAI-1 is augmented in aged mice with endotoxemia, which is linked to suppressed fibrinolysis and increased thrombosis (190). Age-dependent DIC in the lung and kidney and increased plasma levels of PAI-1 were later confirmed in a murine model of severe acute pancreatitis, an acute systemic inflammatory disease of the pancreas that often leads to sepsis (119). We also found that activation of protein C (PC) is strongly suppressed in aged mice with endotoxemia: This causes insufficient production of a potent anti-coagulation factor, aPC (158, 159). Activation of PC to aPC requires thrombin and thrombomodulin (TM). The insufficient production of aPC is at least partly due to a profound/prolonged downregulation of TM during systemic inflammation in aged animals (159). Similarly, age-associated suppression of aPC production and increased thrombosis was confirmed in an abdominal sepsis model using a cecal ligation puncture (158).

Taken together, two major anti-coagulant mechanisms, fibrinolysis and the PC pathway, are suppressed in aged animals during sepsis, which likely contributes to elevated thrombosis in the aged during sepsis (Fig. 4). We found that several pro-coagulant factors such as tissue factor, thrombospondin-1, PAI-1, and PAI-2 are strongly expressed in VAT during systemic inflammation, with higher levels observed in the aged, suggesting a pathophysiological role of fat tissue in age-dependent coagulation (154). Our recent work utilizing patient-derived visceral fat specimens has demonstrated a role specifically for adipose tissue-derived PAI-1 in the development of acute kidney injury in septic patients (194).

Oxidative Stress

During the inflammatory response, neutrophils undergo a respiratory burst and produce superoxide ($O_2^{\bullet -}$). The superoxide anion reacts with nitric oxide (NO) and produces a

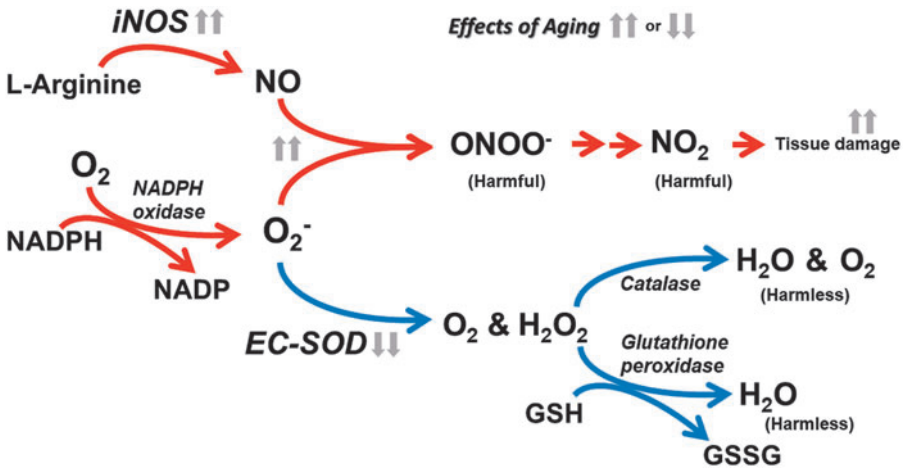

FIG. 4. Two mechanisms for age-dependent enhancement of coagulation during sepsis. (i) Suppression of the PC pathway: Sepsis or systemic inflammation causes conversion of pro-thrombin to thrombin, which converts fibrinogen to fibrin, leading the blood to clot. Although thrombin stimulates positive feedback mechanisms to enhance coagulation by activating factors V and VIII to further produce thrombin, it also acts as a negative feedback mechanism called the PC anticoagulant pathway. In this pathway, thrombin, with its cofactor TM, converts PC to aPC. The produced aPC negatively regulates coagulation by inactivating factors Va and VIIIa. However, in aged animals, sufficient production of aPC is blocked during sepsis and endotoxemia, leading to increased coagulation (158, 159). The reduced aPC production is likely due to age-dependent reduction of TM expression during acute inflammation (159). (ii) Suppression of fibrinolysis: Plasmin is an anti-coagulation factor that degrades cross-linked fibrin (blood clots). PAI-1 inhibits conversion of plasminogen to active plasmin. PAI-1 production during sepsis and systemic inflammation tends to be augmented in aged animals, causing a reduction of plasmin-mediated fibrinolysis and resulting in increased accumulation of blood clots (119, 159, 189). aPC, activated protein C; PAI-1, plasminogen activator inhibitor 1; PC, protein C; TM, thrombomodulin.

toxic peroxynitrite ($ONOO^-$). The production of ROS and reactive nitrogen species (RNS) are typically balanced by antioxidants to prevent tissue and organ damage.

Superoxide dismutases (SODs) are the only antioxidant enzymes that can scavenge $O_2^{\bullet-}$. Among three distinctively different SODs, only extracellular SOD (EC-SOD or SOD3), but not CuZnSOD (or SOD1) and MnSOD (or SOD2), is localized extracellularly to scavenge free radicals. This enzyme is predominantly expressed in the lung and protects animals from systemic inflammation by reducing oxidative damage (173). Expression of EC-SOD is temporarily downregulated on systemic inflammation in young animals; however, such downregulation is significantly more profound and prolonged in aged mice (160). Aged animals also show significantly augmented iNOS expression in the lung during systemic inflammation, suggesting an overproduction of NO. The combination of reduced EC-SOD expression and augmented NO production in the aged appears to cause an overproduction of peroxynitrite, resulting in pulmonary injury (Fig. 5) (160).

In human studies, plasma SOD and catalase are significantly decreased in sepsis patients when compared with healthy, nonsepsis controls (91). The ''plasma SOD'' as stated in the article is likely to be EC-SOD. Importantly, low plasma SOD and catalase levels were associated with lower levels of creatinine clearance, linking the decrease of two enzymes during sepsis pathogenesis with decreased kidney function (91). In plasma samples from sepsis patients, the ratio of the oxidized form of coenzyme Q10 to total coenzyme Q10 is increased when compared with nonsepsis human controls, indicating that oxidative stress increases during sepsis pathogenesis (100). In the same study, the plasma concentration of antioxidant ascorbic acid was significantly decreased in sepsis patients (100).

Age-associated increases in coagulation and oxidative damage can further exaggerate systemic inflammation (193). Indeed, the oxidative stress theory of aging attributes the accumulation ROS and RNS as a source of functional issues and presentation of age-related comorbidities, such as cardiovascular disease, COPD, and cancers (188). As a result, it is likely that these conditions promote organ failure and possible resulting death, especially in older individuals (Fig. 6).

Sex hormones

Sex hormones also appear to play a role in sepsis progression and mortality. Nasir *et al.* found that males had a relative risk of mortality of 1.73 with a mortality rate of 46% compared with a 27% mortality rate in females (114). The more favorable outcomes in females may, in some part, be due to differences in sex hormones (24). Estrogen and estradiol are of particular note, as they have roles in jump-starting the immune response, improving vascular responsiveness, and reducing apoptosis and inflammation through anti-inflammatory cytokines (24, 143). Schroder *et al.* found that testosterone levels were diminished in male sepsis patients, whereas testosterone levels in females fell in the normal range (143). Lower testosterone levels have been reported to accompany sepsis, burns, and shock (143). However, testosterone does not appear to have a protective effect, and the administration of testosterone to female mice

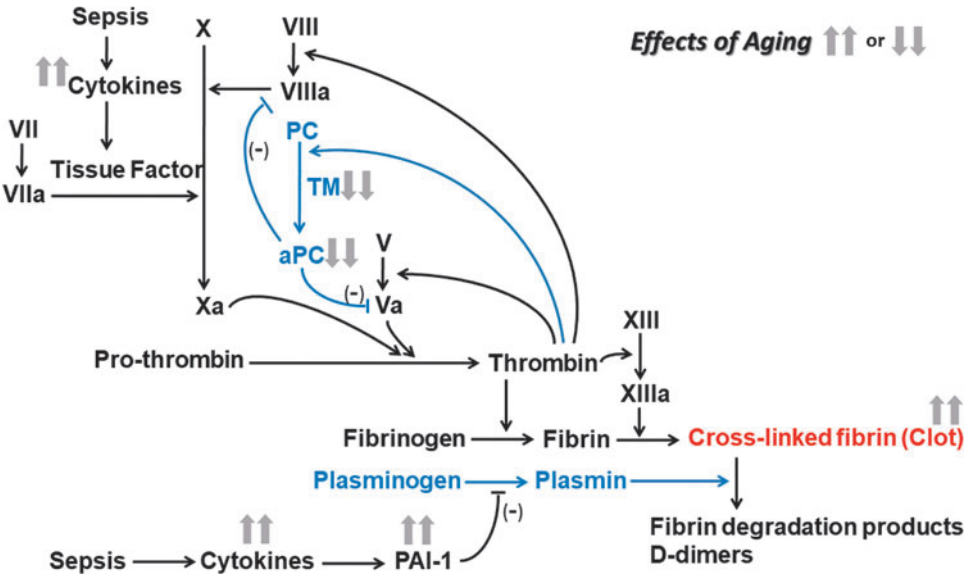

FIG. 5. Mechanisms for age-dependent increase in oxidative damage during sepsis. Sepsis triggers respiratory burst of neutrophils that produce superoxide ($O_2^{\bullet-}$). During sepsis, iNOS is upregulated and produces NO. $O_2^{\bullet-}$ and NO form biologically harmful peroxynitrite ($ONOO^-$), which is converted to even more harmful NO_2. EC-SOD is an anti-oxidant enzyme that negatively regulates the production of peroxynitrite ($ONOO^-$) by scavenging superoxide ($O_2^{\bullet-}$) and converting it to harmless molecules (*blue lines*). In young healthy animals during sepsis, EC-SOD is temporally downregulated, thus producing a certain limited amount of harmful radicals that function in host defense against microorganisms (172). In aged animals, expression of iNOS is significantly augmented whereas EC-SOD downregulation is more profound and prolonged. Such age-dependent changes cause excessive production of harmful $ONOO^-$ and NO_2, which contributes to protein/tissue damage and resulting organ dysfunction (160). EC-SOD, extracellular superoxide dismutase; iNOS, inducible nitric oxide synthase; NO, nitric oxide; NO_2, nitrogen dioxide.

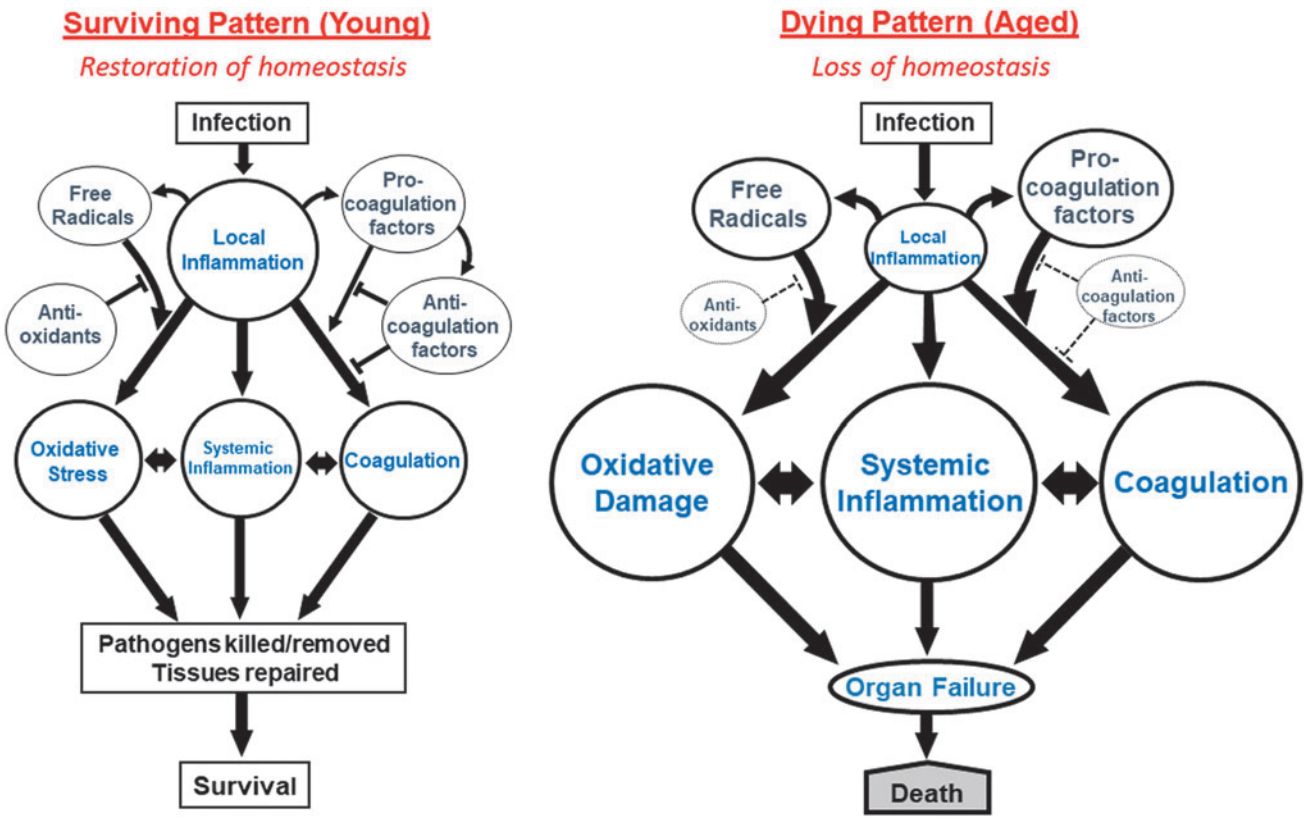

FIG. 6. Differential sepsis progression in surviving *versus* dying patterns. When a young, healthy individual is infected, local inflammation triggers free radical production to control pathogens, but the free radicals are well regulated by anti-oxidants. Local inflammation drives the production of pro-coagulation factors that are regulated by anti-coagulation factors, preventing excessive coagulation. Therefore, oxidative damage, coagulation, and systemic inflammation are well regulated to the minimum necessary levels that are sufficient for controlling pathogens, leading to the restoration of homeostasis and subsequent survival (*left*). In aged individuals, production of free radicals and pro-coagulation factors are often augmented, partly due to insufficient anti-oxidants and anti-coagulation factors. This results in augmented oxidative damage and coagulation, which cause enhanced systemic inflammation, all of which lead to a condition with a ''loss of homeostasis'' driving organ failure and resulting death (*right*).

actually drove immunosuppression (143). Administered forms of estrogen and estradiol show promise in mediating neuronal degeneration and hemorrhagic shock (24).

Furthering the notion that sex hormones play an important role in how individuals respond to sepsis are the promising results of administering estradiol in male rats after trauma (87). Testosterone and other male androgens have been shown to depress the immune system's response, with their supplementation in female mice leading to marked immunosuppression (143). Despite this promise, evidence of estrogen serving as a protective feature is lacking in the clinical setting, possibly a function of the higher age of most sepsis patients.

Future Considerations

Increasing knowledge

A majority of elderly patients have multiple comorbidities, and each of them potentially negatively affects sepsis outcomes. Due to insufficient information regarding the effect of comorbidities on sepsis pathophysiology, the available treatment options for patients are limited. Expanding our knowledge in the pathophysiology of older sepsis patients is urgent. By promoting the establishment of sepsis biospecimen repositories and high-throughput analyses of patient-derived materials, we can begin to fill this knowledge gap.

Wide-spectrum treatment

When it comes to treating sepsis, combined therapy may be essential since sepsis involves multi-organ dysfunction. Several pathways are involved in sepsis, including local and systemic immune responses, oxidative stress, coagulation, glucose metabolism, fatty acid metabolism, the complement system, and the acute phase response. Likely a result of the combined involvement of the pathways described earlier, no singular biomarker has been identified to definitively diagnose sepsis (124). Accordingly, clinical trials focusing on a single pathway of a single organ are not likely to be effective in treating sepsis. Attempts to develop a single drug to treat all types of sepsis appear to be unrealistic, as this condition is caused by different types of pathogens (such as a variety of bacterial strains, viruses, and fungi) that target different sites of infection (such as pulmonary, abdominal, urinary tract, skin, *etc.*). Further, as the majority of sepsis patients are older adults, most of whom carry varying comorbidities (Fig. 3),

sepsis treatment strategies should be carefully chosen with consideration for each patient's specific set of conditions.

Recombinant aPC (Drotrecogin α or Xigris [Eli Lilly & Co.]) was developed for the treatment of sepsis because aPC has multiple functions—it is an anti-coagulant, and it also serves as an anti-inflammatory and anti-apoptotic mediator. However, despite an initial promising result, the drug was withdrawn in 2011 due to the lack of a survival benefit and an increased risk of bleeding (14, 132).

Recombinant human thrombomodulin (rh-TM) (ART-123 or Recomodulin) is another anti-sepsis drug primarily targeting the PC pathway (Fig. 4) and possesses multi-protective functions similar to aPC. A Japanese study (2011–2013) reported promising results that treatment with rh-TM reduced sepsis mortality significantly without increasing bleeding complications (66). A more recent large international study (2012–2018), however, did not find a statistical significance to support the efficacy of rh-TM for increasing sepsis survival (175). Some controversy exists as to whether significantly improved survival rates would have been observed if sepsis patients were more adequately selected for rh-TM treatment (189). Although the data are still inconclusive, further studies on rh-TM treatment are anticipated (79).

Appropriately aged animals in preclinical research

It is widely recognized that many sepsis treatments developed from animal models never successfully rescued sepsis patients (135). One of the reasons, and possibly the foremost one, is the fact that although the majority of sepsis cases occur in the geriatric population, most laboratory animals used for sepsis research are very young (47, 155). As compared with young mice, aged mice are frail, have comorbidities, and are difficult to rescue from experimental sepsis by any treatments. Our study demonstrated that in contrast to aged mice, young mice do not exhibit coagulopathy during sepsis despite an increase in the circulating level of coagulation markers (158). This highlights an example of the discrepancy between young septic mice and aged septic mice, the latter of which more closely mimics sepsis patients. Although the use of young rodent animals for research is highly practical due to availability and low cost, any potential therapeutic intervention for sepsis derived from the study of young animals should be confirmed by using appropriately aged animals.

Clinically relevant ICU-like setting

Another reason for the failure of preclinical studies to be translated to clinical improvements is a lack of clinically relevant experimental design. A majority of sepsis deaths occur in the ICU where patients are treated with fluids and antibiotics, whereas most animal research does not include such treatments (67). In humans, the timing and duration of antibiotic intervention are important (49, 174). Delaying antibiotic intervention increases mortality by nearly 1% per hour, and waiting 6 h from sepsis development increases the risk of death 8.5% compared with starting treatment within an hour (49). When comparing antibiotic administration *via* intravenous infusion for long or short periods of time, prolonged administration resulted in a 30% lower risk of death once sepsis severity was accounted for (174).

Our laboratory has recently demonstrated that a combined therapy of antibiotics and fluids (starting 12 h after sepsis induction, repeated twice a day for 5 days) can rescue nearly 75% of late-middle-aged C57BL/6 mice (16 months old, equivalent to ~50-year-old human) from otherwise completely lethal (LD100) sepsis (121). It is important to mention that therapeutic resuscitation should not be initiated too early after infection, as such practice will prevent sepsis development in animals (161).

Numerous studies have reported successful drug treatments that improved survival rates impressively in rodent models of sepsis without any fluids and/or antibiotics resuscitation. Had this kind of resuscitation been included, survival would have increased significantly, and thus the beneficial effects of the drugs would be completely masked by the resuscitation effects. Thus, for preclinical therapeutic studies, we recommend including ICU-like resuscitation procedures. Drug efficacy should test whether candidate treatments can further improve the survival beyond the antibiotics/fluids resuscitation.

Understanding COVID-19 in relation to sepsis

The novel coronavirus 2019 (COVID-19) is caused by infection with a newly discovered coronavirus (called SARS-CoV-2). Severe COVID-19 may be considered as viral sepsis, and some patients diagnosed with COVID-19 meet the Sepsis-3 definition (20). A study reported that sepsis accounted for 18% of COVID-19 deaths (178). Many symptoms that are characteristics of COVID-19—fever, tachypnea, hypercoagulability, and the release of proinflammatory cytokines—are consistent with typical sepsis symptoms (20).

Similar to sepsis, COVID-19 hospitalizations and mortality rates increase with age. Further accumulation of data will reveal the similarities and differences of sepsis and COVID-19 and how aging impacts survival in these similar conditions.

Authors' Contributions

All authors have provided substantial contributions to the conception or design of the work; the acquisition, analysis, and interpretation of the data. All authors have contributed to the drafting and revising of the work critically for important intellectual content; they have approved the final version being submitted. The corresponding author assumes the responsibility for being accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Author Disclosure Statement

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Abbreviations Used

aPC = activated protein C
CLP = cecal ligation and puncture
COPD = chronic obstructive pulmonary disease
DIC = disseminated intravascular coagulation
EC-SOD = extracellular SOD (or SOD3)
ICU = intensive care unit
iNOS = inducible nitric oxide synthase
LPS = lipopolysaccharide
NK = natural killer
NO = nitric oxide
NO_2 = nitrogen dioxide
PAI-1 = plasminogen activator inhibitor 1
PC = protein C
PICS = persistent inflammation/immunosuppression and catabolism syndrome
rh-TM = recombinant human thrombomodulin
RNS = reactive nitrogen species
ROS = reactive oxygen species
SODs = superoxide dismutases
T1DM = type 1 diabetes
T2DM = type 2 diabetes
TLR = Toll-like receptor
TM = thrombomodulin
VAT = visceral adipose tissues