

Understanding Post-Sepsis Syndrome: How Can Clinicians Help?

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Abstract: Sepsis is a global health challenge, with over 49 million cases annually. Recent medical advancements have increased in-hospital survival rates to approximately 80%, but the escalating incidence of sepsis, owing to an ageing population, rise in chronic diseases, and antibiotic resistance, have also increased the number of sepsis survivors. Subsequently, there is a growing prevalence of “post-sepsis syndrome” (PSS). This syndrome includes long-term physical, medical, cognitive, and psychological issues after recovering from sepsis. PSS puts survivors at risk for hospital readmission and is associated with a reduction in health- and life span, both at short and long term, after hospital discharge. Comprehensive understanding of PSS symptoms and causative factors is vital for developing optimal care for sepsis survivors, a task of prime importance for clinicians. This review aims to elucidate our current knowledge of PSS and its relevance in enhancing post-sepsis care provided by clinicians.

Keywords: post-sepsis syndrome, sepsis, long-term outcome

Introduction

Sepsis is defined as a dysregulated host response to infection and is a leading cause of death worldwide, affecting over 49 million people and causing approximately 11 million deaths annually¹ - a concern that the World Health Organization recognizes as a global health priority.² Notably, these figures only include in-hospital deaths; the outcome of the other 38 million sepsis survivors discharged from the hospital varies significantly. The mortality rate within one year after hospital discharge ranges between 7% and 43%³ and five-year mortality rates after sepsis are between 44% and 82%.⁴⁻⁶ Due to the ageing population, increased prevalence of chronic diseases and antibiotic resistance, the incidence of sepsis is rising and thereby also the number of sepsis survivors.

The rising number of sepsis survivors warrants the need for appropriate care after sepsis. Around 75% of sepsis survivors develop at least one new medical, psychological, or cognitive diagnosis after hospital discharge.⁷ Only half of the sepsis survivors (both ICU and non-ICU) achieve complete or near-complete recovery within two years after hospital discharge.⁸ On the other hand, one in six patients experiences persistent impairments.⁸ As such, sepsis survivors are at risk for rehospitalization, recurrent infections and chronic illness and have a shorter life expectancy, and lower quality of life.⁹⁻¹⁴ Therefore, there is a need to increase awareness for the so-called “post-sepsis syndrome” (PSS): a constellation of long-term physical, medical, cognitive, and psychological issues following sepsis recovery that puts survivors at risk for hospital readmission, and is associated with a reduction in health and life span.

Within the first 30 days following hospital discharge, one in five sepsis survivors is readmitted to the hospital and one in three is readmitted within 90 days.^{9,15} Recurrent sepsis is the leading diagnosis for 30-day readmissions, accounting for almost one-third to half of them.^{11,15,16} Other common complications are pneumonia, kidney failure,¹⁷ heart and

respiratory failure.^{11,15} Notably, sepsis survivors have a significantly increased risk of cardiac events up to 5 years after the sepsis episode as compared to age-/sex-matched population control subjects.^{18–21} Together, post-sepsis complications increase healthcare utilisation and societal burden.²²

Additionally, many sepsis survivors struggle with physical and cognitive dysfunctions after sepsis. Compared to age-matched controls, individuals who survive sepsis have a decrease in health-related quality of life (QoL), particularly in the physical domain, persisting for at least five years following discharge.¹⁴ Moreover, almost 60% of severe sepsis survivors have worsened cognitive and/or physical function persisting at least 8 years after hospital discharge.²³ This decline in physical function becomes evident during walking and taking the stairs amongst others, which results in limitations in carrying out routine daily activities.²⁴ These consequences extend to their professional lives, with nearly half of previously employed sepsis survivors unemployed after recovery from an ICU-admitted sepsis episode.²⁵

(Tentative) Definition and Pathophysiology of Post-Sepsis Syndrome

Post-sepsis syndrome can manifest in various ways including fatigue, weakness, difficulties in memories, anxiety and reduced quality of life.²⁶ Thus, any individual who survived sepsis and is experiencing persistent long-term complaints can be identified as having PSS. PSS is associated with several pathophysiologic mechanisms that negatively affect long-term health and lifespan. These pathophysiologic mechanisms include a complex interplay of immune dysregulation,²⁷ persistent inflammation,²⁷ oxidative stress²⁸ and mitochondrial dysfunction.^{29,30} These pathways of residual risk continue to be active even after the patient has clinically recovered from sepsis and thereby makes them more prone to long-term health problems (Figure 1). PSS shares many similarities with the post-intensive care syndrome (PICS). In fact, 70% of the sepsis survivors suffer from PICS within the first three months after ICU discharge.³¹ Further, long-COVID, which is also referred to as post-acute sequelae of SARS-CoV-2 infection (PASC), shows many similarities with both PICS and PSS.³² The overlap between these conditions in terms of symptoms and patients affected, raises the question whether these should be considered separate entities or whether they represent the same condition. However, it should be noted that PICS per definition affects only patients who had been admitted to the ICU, while PSS can also affect individuals with sepsis who had not been admitted to the ICU. The recent COVID-19 pandemic led to huge numbers of patients

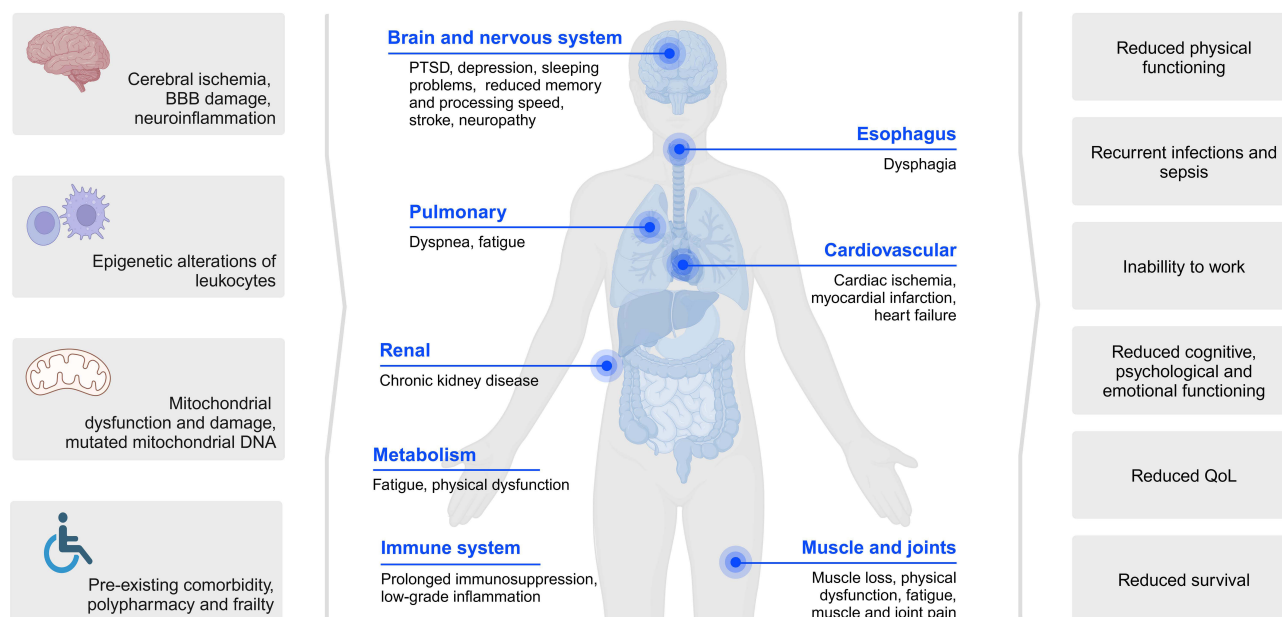


Figure 1 Conceptual model of post-sepsis syndrome.

Notes: Proposed pathophysiological mechanism of PSS, including cerebral ischemia, damage to the blood–brain barrier (BBB), sustained neuroinflammation, immune dysfunction potentially linked to epigenetic modifications in leukocytes, mitochondrial dysfunction and mitochondrial DNA damage, pre-existing comorbidities, polypharmacy, and patient frailty. The manifestation of PSS spans across multiple organ systems, impairing overall functionality, diminishing the quality of life, and potentially curtailing survival rates in post-sepsis scenarios. The figure was created with Biorender and based on our review on the pathophysiology of post-sepsis syndrome.²⁶

Abbreviations: BBB, blood–brain barrier; PTSD, post-traumatic stress disorder; DNA, deoxyribonucleic acid; QoL, quality of life.

suffering from long-COVID syndrome. Although it is unclear whether long-COVID is a different disease entity or represents the same condition as PSS, we deliberately decided to describe the long-term sequelae of sepsis irrespective of the specific pathogen. The long-term consequences after COVID, including potential mechanisms and recommendations, are described in an excellent review by Davis et al and could apply to non-COVID sepsis as well.³³ To our knowledge, there is no specific definition of PSS. Therefore, to facilitate identification of patients at risk for a reduced long-term health and life span, to support research and exchange of knowledge, we propose to use the following definition of PSS: “medical, psychological or cognitive problems arising after sepsis that required hospitalization, that persist weeks to months after hospital discharge, negatively impacts the functioning of the individual and for which no alternative diagnosis can be found”. Insight in the (cause of) long-term symptoms and health problems of PSS is essential to develop personalised post-sepsis care to manage the impact of sepsis and improve long-term outcome. In this review, we summarise important aspects of PSS and explore how clinicians can help to mitigate the health problems that may arise after sepsis.

Mitigating Injury in Sepsis

There are various ways to mitigate the impact of sepsis on long-term morbidity and mortality. Apart from preventing sepsis itself, mitigating injury during sepsis is of utmost importance. Mitigating injury in sepsis involves a multi-pronged approach aimed at treating the underlying infection, supporting organ function, and managing inflammation.^{34–36} It is important to note that the management of sepsis is complex and requires a team-based approach involving critical care physicians, infectious disease specialists, and other healthcare professionals – both for individuals admitted to the intensive care unit (ICU) and those at the general wards. Early recognition and prompt treatment of sepsis are critically important to prevent injury and improve outcomes. Early administration of appropriate antibiotics remains the cornerstone of bacterial sepsis treatment and is essential for infection control, particularly if administered in the critical early hours.³⁴ In addition to source control, providing optimal supportive care is critical to avert organ failure and comprises titrated oxygen therapy to prevent hypoxemia and hyperoxia, fluid resuscitation to stabilise blood pressure while trying to maintain euvolemia and administration of vasopressors as additional blood pressure support.^{35,36} Providing early nutritional support during sepsis is crucial, because sepsis results in increased metabolic demands, marked by a sudden catabolic response that triggers the breakdown of energy stores such as glycogen and lipid stores to facilitate glucose production, leading to rapid muscle loss.^{37,38} Determining appropriate calorie and protein requirements for septic patients can be challenging due to factors such as variations in metabolic rate, changing energy needs over time and between patients, and the potential for underfeeding when energy requirements are underestimated. Individualised caloric goals based on measuring resting energy expenditure using indirect calorimetry are ideal and nutritional screening at different stages of the septic process may be more appropriate than a single approach, as sepsis can impact the feeding process in various ways over time, due to multi-organ failure or gastrointestinal dysfunction amongst others.^{38,39}

Mitochondria play a key role in energy homeostasis in sepsis and mitochondrial dysfunction is a common feature of sepsis that is associated with poor outcome.^{39,40} However, even with the correct administration of calories and nutrients, patients may not be able to process these delivered nutrients when mitochondrial dysfunction occurs. In turn, dysfunction of the mitochondria can lead to impaired cellular metabolism, oxidative stress, and cell death,⁴¹ thereby contributing to multi-organ failure, as well as long-term complications in survivors of sepsis.²⁹ The increased oxidative stress resulting from dysfunctional mitochondria induces damage to lipid, proteins, and DNA and thereby affects mitochondrial integrity. Increased levels of oxidised nucleobases (ie, the building block of DNA and RNA) in sepsis are associated with lower long-term survival after sepsis.⁴² It is unclear whether mitochondrial damage is restored after sepsis. Strategies aimed at improving mitochondrial function may offer potential therapeutic benefits for patients with sepsis.⁴³ Up to this point, interventions that target the renewal of mitochondria or use mitochondria-targeted antioxidants showed promising results in preclinical studies: such interventions can increase energy production (ATP), improve mitochondrial mass, reduce inflammation, and improve survival.^{30,44,45} One of these interventions, for example, is Mdivi-1, a pharmacological inhibitor of mitochondrial fission (ie, a process whereby mitochondria split into two daughter-organelles), which increases membrane potential and ATP production while decreasing ROS generation. The use of Mdivi-1 has been associated with improved survival rates in pre-clinical sepsis models.^{46–48}

Another important factor in mitigating injury is managing inflammation. Sepsis was traditionally considered a hyper-inflammatory syndrome, but there is also an immunosuppressive phase that occurs concurrently with the hyperinflammatory phase.⁴⁹ Immunosuppression is apparent early in sepsis and persists even after the patient is discharged from the hospital.⁵⁰ Prolonged immunosuppression is a significant component of the post-sepsis syndrome, as it appears to be responsible for the high rate of lethal infections and sepsis recurrence.^{9,11,51} Sepsis causes long-term changes in cellular immune function and has a lasting impact on both innate and adaptive immune responses, leading to immune suppression, chronic inflammation, and persistence of bacterial infections.^{9,11} Improving immune function during sepsis and thereby improving long-term outcome have proven to be difficult, and the perfect solution has not yet been found.^{52,53} Considering the heterogeneity of sepsis syndrome and heterogeneity in patients as well, a single-agent approach would probably not work, but rather a combination of different agents, and if possible, personalised per patient in order to achieve the best outcome.⁵³

Preventing Sepsis Recurrence

By prioritising the prevention of sepsis and sepsis recurrence, the number of patients suffering from PSS will be significantly reduced. Important factors in preventing sepsis and sepsis recurrence are antibiotic stewardship programs to prevent antibiotic resistance, hand hygiene, vaccination programs, preventing infections in healthcare settings, attention for nutrition and food, and creating awareness among the population. From these measures, the most important, cost-effective, and uncomplicated way to decrease the prevalence of healthcare-associated infections and antimicrobial resistance is proper hand hygiene.⁵⁴ The combination of interactive educational programs and the provision of hand disinfectants has led to a substantial improvement in hand hygiene compliance.⁵⁴ Another relatively simple measure to prevent some important causes of sepsis is vaccination. Examples of these are the annual vaccinations against COVID-19, influenza and pneumococcal disease.^{55,56} Immunisation has significantly reduced the incidence of bacterial meningitis, pneumonia, and overwhelming infections in children caused by *Haemophilus influenzae* type B and *Streptococcus pneumoniae*, which are the primary pathogens responsible for these illnesses.⁵⁷ Implementing such practices to prevent sepsis can therefore reduce the incidence of PSS. Thus, it is crucial for clinicians to promote and encourage proper hand hygiene practices as well as vaccination among individuals.

Sepsis Awareness

Another important step in early recognition and potentially preventing sepsis is becoming aware of its existence. The awareness of sepsis among the population varies significantly between countries, region, sex, education level and ethnicity.⁵⁸ For example, in an international survey using structured telephone interviews among 6021 interviewees in Europe and the United States, it was found that in Spain, the United Kingdom, Italy, France, and the United States, a mean of 88% of interviewees had never heard of the word sepsis, compared to 47% in Germany.⁵⁹ Of these interviewees who knew sepsis, 58% did not recognize it as a leading cause of death. A Swedish study showed that only 21% of adults knew about sepsis in 2015, however this number has increased to 58% in 2023 according to the Swedish Sepsisfonden.⁶⁰ A Canadian study, which administered an online structured survey to English- or French-literate adults, showed that 39% did not know the word sepsis.⁵⁸ Of the 61% of persons who heard of sepsis, only 25% recognized vaccination as a preventive measure against sepsis.⁵⁸ Furthermore, only 32% were aware of the symptoms and 17% of the risk factors of sepsis.⁵⁸ Ambiguity surrounding the definition of sepsis may be a contributing factor to the low overall unawareness of the condition among the general population.⁶¹ The term “blood poisoning” often used indicates the presence of bacteria in the blood but the fact is that only one-third of sepsis patients have a positive blood culture contributes to the complicity in giving the correct diagnosis.⁶² In response to this unawareness, governments and non-governmental organisations worldwide are arranging major awareness campaigns. One example of this is the World Sepsis Day, first organised in 2012 by the Global Sepsis Alliance and founders.⁶¹ In a scoping review, media and internet were both cited as the most common source to find information about sepsis. People were more inclined to seek information on sepsis when high-profile sepsis-related stories were published, such as the death of a celebrity, which could increase the relative search volume on the internet with 550%.^{63,64} However, despite its prevalence and high fatality rate, sepsis relative search volume on the internet is lower than that of influenza, stroke, and myocardial

infarction, indicating that awareness of sepsis should be improved.⁶⁴ Clinicians could help by stimulating public education campaigns such as the World Sepsis Day⁶¹ and also by creating educational materials like brochures, posters, infographics, and pamphlets that explain what sepsis is, explain its risk factors and describe how to seek help when needed. Efforts made to collaborate with schools and universities to include sepsis awareness lectures in the education curriculum during biology-related classes for example, or create informative social media accounts should be further implemented.⁶⁵

Antibiotic Stewardship

Furthermore, appropriate antimicrobial therapy is an essential part in the management of sepsis. Prompt administration of antimicrobial therapy is crucial in improving patient outcomes, as delays in treatment have been associated with increased mortality.⁶⁶ However, potential unintended consequences of inappropriate antimicrobial prescribing, such as the development of antimicrobial resistance and healthcare-associated infections, are problematic. Antibiotic stewardship programs are important to address this issue, which use strategies aimed at improving the appropriate use of antibiotics. The implementation of antibiotic stewardship programs in hospitals can lead to a significant reduction in antibiotic consumption and rates of hospital-acquired infections such as *C. difficile* infections, without compromising clinical outcomes.⁶⁷ As such, a meta-analysis showed that the risk of hospital-acquired infections was reduced by 48% in studies that included an infection control or hand hygiene program in addition to an antibiotic stewardship program. On the other hand, studies that did not have an infection control program did not show any significant reduction in the risk of hospital-acquired infections.⁶⁷ In addition, antibiotic stewardship programmes significantly decrease the occurrence of infections and colonisation with antibiotic-resistant bacteria and *C. difficile* infections among hospitalised patients.⁶⁸ Another systematic review and meta-analysis showed that de-escalation therapy and prescribing empirical therapy according to guidelines, two important antibiotic stewardship methods, significantly reduced mortality in hospitalized patients with infection. Guideline-adherent empirical therapy was associated with a relative risk reduction for mortality of 35% and for de-escalation of 56%.⁶⁹ On the other hand, septic patients who are exposed to high-risk antibiotics or receive increased quantities of antibiotics during their hospitalisation have an elevated risk of sepsis within 90 days of discharge.⁷⁰ Thus, antibiotic stewardship programs are important to not only optimise antibiotic use but also decrease the risk of sepsis and sepsis recurrence.^{68,70–73} This necessitates doctors to adhere to existing antibiotic guidelines and exercise thoughtful consideration before administering antibiotics.

Physical Complaints After Sepsis

Fatigue

Fatigue is a very common problem after sepsis and is reported in two out of three sepsis survivors during the first year after hospitalisation.⁷⁴ Fatigue has a major impact on life, as it also influences the ability to focus during conversations, reading and overall concentration during the day.⁷⁵ A large multinational survey taken among 1731 sepsis survivors within 5 years after hospital discharge demonstrated that one in three survivors was not back to normal pre-hospital health at the time of the survey. Sepsis survivors stated an increase in sensory, integumentary, digestive, breathing, chest pain, kidney and musculoskeletal problems, as compared to pre-hospitalization.²⁴ More importantly, of those sepsis survivors only 5.5% said they felt very well after sepsis.²⁴ Another common feature is (poly)neuropathy, also called critical illness polyneuropathy (CIP), which occurs in 70% of septic patients and up to 100% in patients with multi-organ failure.^{76,77} CIP is a large contributor to muscle weakness and thereby influences quality of life heavily. Thus, recovering from sepsis can be a challenging process, whereby fatigue and exercise intolerance are common symptoms experienced by many individuals. General measures to decrease fatigue such as taking enough time to rest, regularly exercising, stress-managing and supportive care could be helpful in improving symptoms; however, it is important to notice that recovery from sepsis takes time, and everyone's journey is different. Clinicians can play a role in assisting individuals to reduce fatigue and other physical symptoms by giving advice on lifestyle modifications, medication review, education and psychological support.

Dysphagia

Post-sepsis dysphagia is a common complication of which many sepsis survivors suffer from. In a retrospective cohort study in elderly people with sepsis, approximately 17% experienced dysphagia. Of those with dysphagia, 84% did not regain their swallowing function by the time of hospital discharge.⁷⁸ Another retrospective observational study showed that 35% of sepsis survivors had persisting dysphagia after hospital discharge.⁷⁹ Importantly, dysphagia is a well-known risk factor for aspiration and aspiration-induced pneumonia, malnutrition due to delayed resumption of oral intake, reduced quality of life, longer ICU and hospital stays, and heightened morbidity and mortality.⁸⁰ Risk factors for dysphagia are not yet fully discovered since studies are scarce and provide conflicting results. However, most accepted risk factors are duration of intubation and mechanical ventilation.⁸⁰ Thus, it is imperative for survivors of severe critical illness, including sepsis, to undergo otorhinolaryngological evaluation for dysphagia at the time of ICU discharge in order to develop specific swallowing rehabilitation programs. Otorhinolaryngological evaluation is mainly done by a trained speech-language pathologist.⁸¹ Present treatment options for individuals with swallowing impairments include adjusting dietary texture, adopting specific postures, implementing compensatory techniques, engaging in therapeutic exercises, and utilising nerve stimulation. With the aid of speech-language pathologists, gastroenterologists, otolaryngologists, dietitians and neurologists, critical care practitioners can employ a collaborative, multidisciplinary approach to establish personalised therapies for each patient.^{82,83}

Muscle Loss and Physical Dysfunction After Sepsis

Classification strategies of multiple-organ failure (MOF) in critically ill patients have historically centred on the most clinically obvious organ dysfunctions, primarily the pulmonary, renal, and cardiovascular systems.^{84,85} However, other peripheral organ systems, such as skeletal muscle, are also affected in patients who survive the initial septic event.⁸⁶ Although wasting of skeletal muscle in critically ill patients was originally described approximately 5 decades ago,^{87–89} the acuity and magnitude of muscle wasting and weakness have been rediscovered and re-emphasized.^{90,91} For example, Puthucherry et al demonstrated a 15% reduction in rectus femoris muscle cross-sectional area within 7 days in patients with MOF, associated with muscle protein synthesis/catabolism imbalance.⁹¹ Pre-existing lower muscle mass (sarcopenia)⁹⁰ and lower fat mass⁹² may contribute to poor clinical and functional outcomes after sepsis.

Significant and long-lasting functional defects are well described among survivors of critical illness, which may be the effect of acute and chronic muscle wasting, and amplified by greater age.^{93,94} For example, compared to the young patients, older surgical sepsis patients had poorer functional status and objectively measured physical function and handgrip strength after 12 months of follow-up.⁹³ In addition, older patients remained persistently inflamed with ongoing catabolism.⁹⁵ While a combination of bed rest and neurologic (dysregulation of neural inputs at the neuromuscular junction), hemodynamic (hypoperfusion) and molecular pathologic factors (mitochondrial and satellite cell dysfunction, and protein breakdown) likely play a role, the underlying mechanisms of the ICU-acquired weakness and long-term functional disability remain poorly understood.⁹⁶ We will limit our discussion to local skeletal muscle-related mechanisms that contribute to muscle wasting and weakness.

Mitochondrial and Satellite Cell Dysfunction as Major Biological Mechanisms of Muscle Wasting

In addition to the detrimental effect of bed rest and muscle disuse on muscle mass,⁹⁷ sepsis-induced skeletal muscle catabolism reflects impaired satellite cell and mitochondrial functions, increased proteolysis, decreased protein synthesis and release of degradation products that have pro-inflammatory features as damage-associated molecular patterns (DAMPs) from skeletal muscle mitochondria.^{30,96,98,99} Satellite cells are the muscle stem cells and a proper function is essential for muscle repair in response to factors such as injury and exercise.³⁰ When activated, satellite cells turn from the quiescent state to start forming myotubes.³⁰ Satellite cells are required for maintenance of lean mass as demonstrated in a mouse model of sepsis, but its function declines in response to sepsis.^{30,99} Transcriptomic changes of satellite cells induced by sepsis in mice were persistently changed at day 28 after sepsis compared to control, reflecting impaired energetic pathways representing oxidative phosphorylation and mitochondrial dysfunction. These observations reflect impaired satellite cell function and reduced muscle repair.⁹⁹ The detrimental effect of mitochondrial and satellite cell

dysfunctions on the maintenance of muscle energetics and repair warrant further research to develop strategies to target sepsis-induced muscle catabolism state with relevance to prevent muscle loss and functional decline after sepsis.

Exercise Training and Nutrition as a Non-Pharmacological Treatment of Sepsis-Induced Physical Dysfunction

Exercise training, including aerobic and resistance exercise, is one of the most powerful interventions to gain and maintain skeletal muscle mass, skeletal muscle quality and overall physical function.¹⁰⁰ Early rehabilitation aimed at maintaining muscle mass and cardiopulmonary function is important to facilitate recovery from critical illness.^{101,102} However, anabolic resistance and systemic inflammation associated with sepsis may prevent patients from obtaining improvements in the clinical setting. In particular, anabolic resistance is caused by the altered protein homeostasis, which is in turn amplified by intramuscular inflammation and bioenergetic failure from disrupted substrate use.¹⁰³ Early movement in the ICU has therefore variable results. For example, electrical stimulation of both lower and upper limbs over 5 days in the ICU attenuated muscle loss and proteolysis, but there was no difference in muscle weakness.¹⁰⁴ Additionally, electrical stimulation applied within the first 72 hours after ICU admission did not lead to muscle contractile response, but the responsiveness dependent on the disease severity and differed between responders and non-responders.¹⁰⁵ Electrical stimulation appears more effective in increasing muscle oxygen uptake, as compared to no effect of passive movements.¹⁰⁶

The effects of post-ICU exercise training on functional exercise capacity or health-related quality of life remain unclear due to variability in intervention protocols and inter-personal heterogeneity.¹⁰⁷ Since the anabolic resistance may be the reason for inter-personal heterogeneity in the response to exercise training in the ICU and post-discharge, there is a need for appropriate nutritional strategy related to nutrients and timing in order to stimulate anabolism.¹⁰⁸ Early enteral or parenteral nutrition improves overall ICU outcomes, although most beneficial effects are seen with multimodal interventions combining different modalities of exercise training and nutritional regimens to preserve skeletal muscle mass in the ICU and prevent functional decline post-discharge.¹⁰⁹ For example, the ExPrES study showed preservation of lower-limb muscle mass by a 14-day multimodal intervention including muscle electrical stimulation, high-protein supplementation and mobility and strength rehabilitation.¹¹⁰ In contrast, addition of a metabolite of leucine (β -Hydroxy- β -methylbutyrate) to the standard nutrition therapy in combination with electrical stimulation did not reduce muscle loss.¹¹¹ Currently, there are no existing personalised approaches to improve sepsis survivors' health status and physical function in-hospital and once they return home. To our knowledge, most clinical trials focusing on exercise training¹¹² and nutrition (eg, protein supplementation)^{113–115} to preserve muscle strength and physical function showed variable results or failed because of the lack of understanding of the pathology and heterogeneity of sepsis-induced physical disability.^{116,117} Clinicians can play a pivotal role in enhancing the outcomes of sepsis survivors by advocating for and facilitating early rehabilitation, promoting patient-specific exercise and nutritional strategies, and actively participating in the design and execution of personalised care plans. Further, they can contribute to the advancement of our understanding of sepsis-induced physical disability through their involvement in clinical research, facilitating the development of evidence-based personalised approaches to prevent muscle wasting and mobility disability after sepsis.

Cardiovascular Disease

There is a strong correlation between sepsis and several aspects of cardiovascular disease (CVD). Firstly, pre-existing cardiovascular conditions are risk factors for sepsis.¹¹⁸ Secondly, cardiovascular complications such as septic cardiomyopathy are important during the acute phase and contribute to organ dysfunction.¹¹⁹ Thirdly, cardiovascular complications may occur in the post-acute phase after sepsis, both in the first period post discharge and up to several years later. The cause of the increased risk of cardiovascular complications after sepsis is probably multifactorial, including persistent inflammation or immunosuppression, neurohumoral activation, mitochondrial dysfunction, endothelial dysfunction, accelerated atherosclerosis and plaque instability.²⁷ Also, the deprescription of beneficial primary or secondary preventive cardiovascular disease treatments during the acute sepsis episode may contribute to worsening of symptoms or disease progression.¹²⁰

A meta-analysis of 27 observational studies demonstrated an elevated risk of both short- and long-term cardiovascular events (myocardial infarction, stroke, heart failure) and death after hospitalisation for sepsis, with pooled adjusted HR

values of 1.65 to 1.77.¹²¹ The increased risk persisted for at least 5 years. However, there was a large variability across the studies, and some of the included studies were of low quality and had methodological drawbacks. Two recently published large studies further confirmed the link between sepsis and cardiovascular risk. The first study, including 250,000 sepsis survivors without pre-existing CVD, demonstrated a 1.3-fold increase in the hazard of major CVD events (myocardial infarction, stroke or cardiovascular death) up to 5 years of follow-up, compared to matched non-sepsis hospital survivors.¹²² The second study included approximately 2,250,000 patients with increased risk of CVD events who survived a non-surgical hospitalisation, of which approximately 800,000 patients had sepsis.²⁰ The study showed an increased risk of hospitalisation for cardiovascular events in sepsis patients compared to non-sepsis patients (adjusted HR = 1.43). Findings from these two later studies also show that although the absolute risk for an event after sepsis is higher in older patients or in patients with a higher risk profile, the relative increase in CVD risk due to sepsis is higher in younger patients and in patients with few other risk factors for CVD.^{20,122}

Heart failure is the most common cardiovascular event requiring readmission after sepsis.^{11,20} Sepsis patients have an up to a six-fold higher risk of developing atrial fibrillation compared to hospitalised patients without sepsis.¹²³ The diagnosis of atrial fibrillation associated with sepsis could be either a newly developed arrhythmia or the detection of sub-clinical pre-existing atrial fibrillation. Atrial fibrillation development increases the risk of in-hospital stroke up to three times in sepsis patients.¹²³ However, since there is also an increased risk of bleeding, anticoagulants are not generally recommended during the acute phase.¹²⁴ Other studies showed that up to 36–61% of the patients with atrial fibrillation during sepsis have recurrent episodes of atrial fibrillation post-sepsis and an increased risk of stroke up to several years after the sepsis episode, with an adjusted HR of 1.22–1.91 as presented in a recent review by Induruwa et al.¹²⁴ Another recent review and meta-analysis have addressed the long-term risk of cerebrovascular events following sepsis hospitalisation, showing an HR of 1.8 for ischemic or hemorrhagic stroke.¹²⁵ Therefore, it is important to acknowledge that sepsis is a (non-traditional) risk factor for cardiovascular disease, both atherosclerotic and non-atherosclerotic (ie, heart failure and arrhythmias), and an episode of sepsis should be considered to be an important event in a patient's medical history. Considering this, clinicians should offer personalised information to patients in order to enhance their understanding of potential signs and symptoms associated with cardiovascular disease.

Cardiovascular Risk Management and Stratification

According to Surviving Sepsis Campaign, there is insufficient evidence to make a general recommendation on early post-hospital discharge follow-up compared to routine post-hospital discharge follow-up for sepsis patients. However, early follow-up might be beneficial, as studies showed that early follow-up of other patient groups, such as elderly patients and patients with congestive heart failure, is associated with reduced hospital readmissions.^{126,127} Especially early in the post-discharge period it is valuable to reassess the need and dosage of cardiovascular pharmaceutical treatments, considering that deprescription during hospital care is common, and the dosage requirements may be different due to changes in body weight, renal function and cardiac function.^{8,120} Also, evaluating clinical symptoms and signs such as body weight, blood pressure, heart rate and oxygen saturation is important in order to avoid potential reasons for readmission.

Clinicians offering post-sepsis care should maximise their efforts to prevent the development or mitigate the progression of cardiovascular disease by optimising guideline-directed pharmacological and non-pharmaceutical therapies, such as smoking cessation and lifestyle recommendations, monitoring and treatment of hypertension and hyperlipidemia, and the addition of antithrombotic therapy in those with established atherosclerotic cardiovascular disease.¹²⁸ Performing cardiovascular risk factor stratification in patients with pre-existing cardiovascular disease or with known cardiovascular risk factors, as well as in younger, otherwise healthy patients is important to tailor cardiovascular risk management to the needs of the individual patient. Pharmacological preventive interventions such as beta blockers, statins and acetylsalicylic acid could be considered to lower cardiovascular complication risk after sepsis, but large studies providing supporting evidence for these strategies are missing, and they can therefore currently not be recommended on a general basis. Although there is an increased risk for ischaemic stroke in the long-term perspective in patients with sepsis-driven atrial fibrillation, current guidelines offer no recommendations on anticoagulation therapy once they have recovered from sepsis. Outside of guidelines, as Induruwa et al suggest, clinicians may consider offering tailored anticoagulation therapy in a patient-centred care setting¹²⁴ after careful assessment of the risk of ischaemic stroke and haemorrhagic complications using the CHA2DS2-VASc and HAS-BLED scores. As a minimum, patients should be informed of the symptoms of a new episode of atrial fibrillation and if such symptoms occur they should be examined for the existence of

recurrent atrial fibrillation. Early physical rehabilitation could well allow the patient to remobilize after sepsis to maintain an active, healthy lifestyle that is associated with a lower risk of cardiovascular events. Sepsis survivors mention prompt rehabilitation after discharge, physiotherapy and sports as important aspects that should be addressed to improve post-sepsis care,¹²⁹ all of which could be stimulated by clinicians.

Psychological and Emotional Impact

Cognitive Problems After Sepsis

To date, there is limited information on the impact of sepsis on cognitive functioning. Delirium is most common in severely ill sepsis patients, as compared to patients without sepsis at the ICU.¹³⁰ Studies describing the effect of sepsis and delirium on long-term cognitive function seem contradictory, as a study in 125 ICU patients with severe sepsis did not find a relation with either sepsis or delirium and self-rated cognitive dysfunction at 3 months after hospital discharge.¹³⁰ However, another study among 516 severe sepsis survivors and 4517 patients who had been hospitalized for another reason demonstrated a substantial decline in cognitive function at 1 year after hospital discharge as compared to baseline. The incidence of moderate-to-severe cognitive impairments increased by 10% after sepsis and persisted for at least 8 years after sepsis.²³ In line with these observations, neonatal sepsis and sepsis in paediatric patients were associated with neuromotor developmental impairments and new neurological disabilities.^{131,132} The pathophysiology of cognitive impairment in sepsis remains incompletely understood. Yet, several mechanisms have been put forward that appear to underlie cognitive dysfunction after sepsis, including blood–brain barrier (BBB) disruption, neuroinflammation resulting from a BBB disruption and over-activation of microglia and astrocytes, neurotransmitter dysregulation, and neuronal loss. Like dementia, this cognitive impairment is often irreversible, significantly impacting patient quality of life.¹³³ Therefore, clinicians should be alert to these sequelae and act promptly. Although targeting the processes driving cognitive changes in sepsis seems pivotal in preventing or treating cognitive impairment, further studies are needed to expand our fundamental knowledge about the pathophysiology of sepsis-induced cognitive dysfunction and to develop effective treatment strategies.

Psychological Problems After Sepsis

Although reduced QoL after severe illness, like in PSS and PICS, is most prominently linked to long-term physical health complaints, the psychological and emotional consequences are relatively unexplored. Sepsis survivors mention that there is a need for psychological care as one of the unmet needs after hospital discharge.¹²⁹ The impact of critical illness can reflect in several mental health-related problems, like symptoms of PTSD, anxiety or depression with or without cognitive impairment, as described in several studies in survivors of critical illness, independent of sepsis admission status.^{134,135} Risk factors like treatment-related stressors may leave patients vulnerable to develop long-term mental and cognitive health problems which can last for years.^{136,137} Sepsis as primary admission diagnosis was an independent risk factor of stress disorders after critical illness, but specific information on the role of mental health problems within the PSS is lacking.^{138,139} When comparing mental health-related QoL of survivors of severe sepsis to the general population average, the mental component score and/or mental health domain score were significantly reduced in several studies.^{14,140,141} Although the difference in mental health-related QoL is less pronounced than in the physical domain scores, survivors may experience unpleasant memories and recall of ICU events which are often stated as trauma-related symptoms. However, other studies show only a temporary decline in mental health-related QoL or no difference with the healthy control at all.^{142,143} In general, mental health problems such as anxiety, depression, fatigue and sleep disturbances after sepsis are underreported and present in various degrees among the adult patients experiencing PSS.²⁴

Importance of Addressing Psychological and Emotional Complaints After Sepsis

Taking into account the sepsis associated risk factors and long-term outcomes associated with PSS and PICS, the possible vulnerability of the patient group and the possible impact of PSS on the patient and their informal caregivers, addressing psychological and emotional complaints after sepsis in the clinical and primary care setting is essential. Specifically, early screening for and awareness of frailty and impaired resilience may prove effective in identifying patients at risk of PSS.^{144,145} Nevertheless, clinicians may face important challenges during triage practices when it comes to prioritising the rule of rescue over societal benefits and outcomes of patients, as was described in ICU clinicians previously.¹⁴⁶ Awareness of the effects of triage

decisions and case management within the post-sepsis recovery period may be essential for clinicians working with patients suffering from PSS.

In addition, patients and informal caregivers may benefit from multidisciplinary aftercare in the post-hospital period. However, this structure is lacking and patients report dissatisfaction with a number of support services in hospital and after discharge.²⁴ Patients report a lack of psychological counselling, education about sepsis and PSS and social support.²⁴ However, implementing aftercare services can be troublesome due to several barriers. A study on enablers and barriers to implementing ICU aftercare from the Thrive collaboratives showed significant barriers to this included lack of access to clinics, clinic funding, limited attendance by patients and relatives and difficulties in the selection and advertising process.¹⁴⁷ Enablers for successful implementation that were specified involved beneficial infrastructures, flexibility in scheduling and belonging to an international learning consortium. Taking into account these enablers and barriers to provide adequate support for professionals that want to initiate aftercare services is therefore essential, because more structured aftercare services for patients suffering from PSS and PICS are urgently needed. Especially important in making efforts to create “tailor made sepsis aftercare” is involving patients and relatives and ask them what they think can contribute to their quality of life.

Interventions for Emotional and Psychological Support

Although support in the post-sepsis recovery period is scarce for both patients and informal caregivers, increased awareness of PSS may lead to more initiatives for adequate aftercare. One primary care management intervention including training of patients and primary care physicians in evidence-based post-sepsis care, case management by trained nurses and clinical decision support for primary care physicians by consulting colleagues resulted in a decrease of PTSD-related symptoms compared to usual care.¹⁴⁸ However, this study did not find a significant effect on other mental health-related outcomes. Another randomised-controlled trial on a primary care intervention rendered similar results, with no change in mental health-related QoL at six months after ICU discharge.¹⁴⁹ Another RCT that investigated recovery after hospitalisation for sepsis and randomised 291 patients to a multicomponent primary care management intervention or usual care also did not find improvements in mental health-related QoL.¹⁴⁹ One explanation for the limited effect of post-sepsis interventions could be the need to involve the patient’s social support system, as, for example, a partner.¹⁵⁰ When taking a closer look at the general ICU population, there is limited evidence on non-pharmacological interventions. A systematic review showed that the use of diaries and exercise programs during and after admission had a positive impact on mental health outcomes.¹⁵¹ In addition, consultation with a clinical psychologist may help ICU patients with trauma symptoms in their recovery,¹⁵² and supporting caregivers can improve short-term anxiety and depression symptoms.¹⁵³ In conclusion, there is limited support for specific evidence-based interventions to improve mental health in patients suffering from PSS or PICS.

Despite the lack of evidence on interventions to improve mental health outcomes in patients after sepsis, research in other patient groups suggests that patient support programs can be beneficial to improve emotional well-being. For example, an emotional support-focused nursing intervention had a positive impact on psychosocial adjustment of breast cancer patients.¹⁵⁴ In addition, involving family members and loved-ones within the patient journey is valued and appreciated by surgical patients.¹⁵⁵ Also, social support has been found to improve well-being of cognitively impaired elderly individuals.¹⁵⁶ Former sepsis patients mention structural non-medical support frameworks, structures for medical aftercare, financing of aftercare, involvement of relatives and contact point for sepsis aftercare as unmet medical needs after sepsis.¹²⁹ Clinicians can support patients and caregivers by exploring and recommending appropriate (digital) treatments, delivering or referring to generally adopted interventions to treat anxiety and depression, like cognitive behavioural therapy, or incorporate CBT interventions into their care plans.^{157,158} Also referring to peer support groups can help patients find support and reflect on the significance of religion and spirituality in the process, a topic that clinicians often neglect.^{159,160} However, further research with the involvement of experienced experts and patient representatives is needed to investigate support programs specifically targeted towards patients suffering from PSS.

Socio-Medical Aspects of PSS

Surviving sepsis can have far-reaching consequences for patients, and often also their relatives,¹²⁹ beyond the immediate physical and mental impact described in this review. Patients suffering from PSS often face long-term sociomedical consequences that affect their QoL. One of such consequences is difficulty of returning to work, as the toll of PSS can make it problematic to resume

their normal work-related activities. Although studies on the sociomedical consequences of PSS are limited, it has been described that return-to-work rates are similar to those in critical illness survivors, ranging from 60 to 70% up to six years after hospital discharge.¹⁶¹ In addition, sepsis is associated with high morbidity and mortality and survivors usually experience increased healthcare utilisation and financial burden. A retrospective study conducted in the United States found that there was an almost threefold increase in adjusted healthcare utilisation post-sepsis compared to the pre-sepsis levels.¹⁶² The extent of this increase was strongly correlated with the age of the patient at the time of admission. Other patient factors that are already present during admission may have a similar impact on post-sepsis healthcare utilisation, like prior comorbidities and a history of high utilisation pre-sepsis. Similar results have been found in patients surviving critical illness, as sepsis during admission was found to result in higher healthcare resource use and costs compared to matched ICU-patients without sepsis.¹⁶² There are no targeted interventions to improve return-to-work or reduce healthcare utilisation in patients suffering from PSS. However, previously described interventions in similar populations, like patients suffering from PICS, may be a first step to providing tailored aftercare for patients suffering from PSS.

Personalised Post-Sepsis Care

Given the large interindividual differences in clinical presentation and outcomes among patients with an infection and sepsis, a one-size-fits-all approach is unlikely to benefit every patient. Tailoring post-sepsis care to the specific needs of each patient would pose an opportunity to provide effective support by a multidisciplinary team of healthcare professionals (Table 1). To estimate long-term sepsis outcomes and thereby predicting specific needs, pre-existing risk factors for poor long-term outcomes should be considered.⁸ Important to realise is the difference in co-morbidities and frailty in individual patients pre-sepsis, but also the social aspects such as having spouses and a well-functioning social safety net.^{8,163} A promising tool in helping to predict the needs after sepsis is endotype stratification. New research has revealed

Table 1 Possible Multi-Disciplinary Interventions to Improve Recovery in Sepsis Patients by Physiotherapists, Psychologists, Social Workers and Clinicians (Internal Medicine, General Practitioners, Family Doctors and Rehabilitation Physicians Amongst Others)

Description	Examples of Possible Targeted Interventions
Early rehabilitation interventions to improve physical functioning and reduce the risk of disability in sepsis survivors.	Early mobilisation, physical therapy, and occupational therapy interventions.
Cognitive rehabilitation interventions to help improve cognitive function and reduce cognitive impairments in sepsis survivors.	Cognitive training, neuropsychological and neurocognitive rehabilitation, and mindfulness-based interventions.
Psychological support to help reduce symptoms of anxiety, depression, and PTSD in sepsis survivors that can in turn improve their ability to return to work and function in daily life.	Cognitive-behavioural therapy (CBT), mindfulness-based stress reduction (MBSR), Eye Movement Desensitization and Reprocessing (EMDR) therapy and other psychotherapeutic interventions.
Multidisciplinary care involves a team of healthcare professionals working together to provide comprehensive care to sepsis survivors to improve overall functioning and reduce healthcare utilisation.	A multidisciplinary approach to care, including care coordination, discharge planning, and case management.
Medical post-sepsis care comprises (non-) pharmacological measures to optimise the health status of the individual, taking comorbidity, medication use and individual priorities into account, to reduce the risk of (cardiovascular) complications, recurrent infections and lower healthcare utilisation.	Cardiovascular risk management, reducing polypharmacy via medication reviews, vaccinations, (prophylactic) antibiotics, omitting unnecessary use of indwelling urinary catheters or intravenous lines.
Education and self-management to help survivors better understand and manage their ongoing medical needs, and reduce healthcare utilisation.	Providing sepsis survivors with knowledge about their condition and self-management strategies, such as medication adherence and symptom monitoring, but also provide education about adequate hygiene to lower the risk of recurrent infections.
Workplace accommodations by employers to help sepsis survivors return to work gradually and successfully.	Workplace accommodations, such as modified job duties, flexible work hours, and gradual return to work plans.

Note: The text that is highlighted in bold indicates a potential measure to enhance the recovery of individuals with sepsis.

Abbreviation: PTSD, post-traumatic stress disorder.

the possibility of categorising patients with sepsis into different phenotypes based on retrospective clinical data¹⁶⁴ or transcriptome data obtained from whole blood.^{165,166} This type of endotype stratification, utilising clinical and/or molecular data, has the potential to identify patients who may be at higher risk for post-sepsis health problems¹⁶⁵ as well as long-term outcomes.^{164,165} Being aware of potential problems ahead of time allows for timely intervention and mitigation by clinicians.

Current Advice

More information about risk factors is required to select those individuals at risk for poor long-term outcome to be seen by a specialized post-sepsis outpatient clinic for personalized post-sepsis care. Until this information becomes available, it seems most appropriate to invite all patients with sepsis in hospital, either being admitted to the ward or ICU, to a post-sepsis outpatient clinic to be seen by a consultant in general/internal medicine, geriatrics (in case of frail or elderly persons), general practitioner or family doctor. Based on a comprehensive assessment of medical and functional status, a critical review of current (preventive) treatment should be performed with the main aims to lower risk of recurrent infections and cardiovascular disease, lower healthcare use and improve quality of life (Table 2). Former patients indicate information about what to expect after sepsis as a relevant knowledge gap, which should be addressed during the outpatient follow-up.¹⁶⁷ Ideally, given the lack of knowledge about PSS and the information that is required to develop personalized post-sepsis care, the assessment during outpatient follow-up should employ standardized instruments and obtain consent from the patient to use such data for (future) research. Outstanding questions are amongst others: a) how can we identify individuals at risk for poor long-term outcome, who could benefit from personalized post-sepsis care, b) what are effective interventions to improve long-term outcome after sepsis, and c) when should such care be offered?

Table 2 Proposed Content of Post-Sepsis Outpatient Follow-Up by a Clinician

Assessment	Items to Address
Medical	Details of sepsis episode, current health status, co-morbid conditions with special attention to cardiovascular risk factors and co-morbidity. Consider referral to geriatric for CGA in (frail) elderly. Identify risk factors for infection (e.g. urinary catheter, wounds, immuno compromised state) and lower infection risk (eg. vaccination, proper hygiene, removal of indwelling iv-lines and catheters if possible, consider prophylactic antibiotics).
Medication review	All current medications, potential side effects and interactions. Critically review (contra-)indications, assess cardiovascular risk and adjust medication where necessary, while taking frailty and polypharmacy into account as trigger to deprescribe.
Functional assessment	Mobility, activities of daily living, rehabilitation needs and ability for improvement (eg. consider physiotherapy or referral to rehabilitation physician).
Psychological and Cognitive Evaluation	Depression, anxiety, PTSD, cognitive impairment (eg. MMSE), delirium during hospitalization (risk factor for future delirium), mental health support and requirement (eg. consider referral to psychologist).
Nutritional Assessment	Current nutritional status (eg. MUST, SNAQ), dietary advice or interventions (eg. hand out information, refer to online documentation or refer to dietician).
Lifestyle and Social Assessment	Smoking, alcohol and illicit drug use, physical activity, social support network, return to work.
Education	Hand out information or refer to online sources about sepsis (eg. national sepsis society, patient groups) and what to expect after recovery, including the risk of recurrent infection and how to prevent these.
Research	Use standardized instruments to obtain a comprehensive assessment of the medical and functional status of the individual patient, and obtain consent to use these data (and potential other data and/or biomaterials) for (future) research to expand fundamental knowledge about PSS and support the development of personalized post-sepsis care.

Note: The text that is highlighted in bold indicates an example of an assessment for post-sepsis outpatient follow-up.

Abbreviations: CGA, comprehensive geriatric assessment; PTSD, post-traumatic stress disorder; MMSE, mini-mental state examination; MUST, Malnutrition Universal Screening Tool; SNAQ, Short Nutritional Assessment Questionnaire.

Currently available information suggests that the optimal timing for a first follow-up contact would already be within a month after discharge, since one in three sepsis survivors will be readmitted to the hospital within three months, of which the majority is readmitted within one month.^{9,15} However, given that most patients may still receive antibiotic treatment and are recovering in this early phase after hospital discharge (eg, temporary nursing home, physiotherapy) this first follow-up visit can be brief and remote (eg, by telephone or video connection) with the aim to evaluate the effect of actual treatment on recovery. A visit to the outpatient clinic at approximately three months after sepsis allows for a more comprehensive evaluation (Table 2) after the initial recovery phase. Future research should provide insight into the questions addressed above, including the optimal timing and content of the follow-up visits.

Conclusion

In conclusion, sepsis is a life-threatening condition with a rising incidence and consequently, an increasing number of sepsis survivors. These survivors are at increased risk of rehospitalization, recurrent infections, chronic illness, a decline in quality of life and shortening of lifespan. The constellation of long-term physical, medical, cognitive, and psychological issues following sepsis recovery is termed post-sepsis syndrome (PSS). PSS can have major effects on health and life span, potentially precluding previously employed patients to return to work after hospital discharge. Addressing this problem necessitates a comprehensive, multi-faceted approach to improve long-term outcomes for survivors.

The pathophysiology of PSS is complex and far from completely understood. Logically, both pre-existing factors such as co-morbidity, polypharmacy and frailty affect outcome, as well as injury induced by sepsis. Consequently, strategies to mitigate injury during sepsis are key to optimise recovery and will entail early recognition of sepsis to allow timely administration of antibiotics and supportive care, as well as unravelling the pathophysiology to develop targeted therapy to avert organ failure. Recurrence of infections – and sepsis – is a frequently encountered problem and could be curtailed through raising sepsis awareness, increasing vaccination rates, practising good hygiene, and promoting appropriate use of antibiotics to ensure effective antibiotic stewardship, as well as preventing infections by omitting unnecessary use of indwelling urinary catheters or intravenous lines. Given the increased cardiovascular risk in sepsis survivors, it is imperative to manage these risks comprehensively, employing not only pharmacological treatment of common cardiovascular risk factors like hypertension, hypercholesterolemia and diabetes mellitus but also physical rehabilitation, optimised nutrient intake and lifestyle advices (eg, stop smoking, maintain an active lifestyle). Furthermore, it is vital to appropriately address the psychological, emotional and cognitive sequelae of sepsis, for example, by implementing support programs aimed at enhancing emotional well-being and quality of life in the long term. Finally, it should be noted that although new physical complaints after sepsis can be part of PSS, it can also represent another underlying disease. Failure to recover or progressive complaints after sepsis recovery should alert the physician to consider other causes of the complaints.

A personalised, patient-centred approach appears to offer the most promise in managing PSS; however, thus far, no personalized approaches to improve sepsis survivors' health status exist. Managing PSS begins with recognizing and understanding the symptoms, identifying individual risk factors, and elucidating the underlying causes. Such a deep understanding paves the way for selecting patients for specific therapies tailored to their unique needs. Further research is warranted to develop and refine these personalised treatment strategies, with the goal of transforming post-sepsis care and improving the lives of sepsis survivors. More research funding and realisation of centres of expertise that can initiate and coordinate clinical trials can offer sepsis survivors access to novel, potentially effective treatments, before such drugs have obtained market authorization. To this end, it is essential that policymakers realise the societal burden of sepsis and sepsis survivorship.

Acknowledgments

The authors wish to thank I. Nutma, former sepsis patient and chair of the sepsis survivor group “Sepsis-en-daarna” (<https://www.sepsis-en-daarna.nl/>) for critically revising the manuscript.

Funding

This review received no external funding.

Disclosure

The authors declare that they have no competing interests.

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