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REVIEW

Post sepsis syndrome: an ignored enemy

Síndrome post sepsis: un enemigo ignorado

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ABSTRACT

Introduction: post sepsis syndrome is an emerging entity, underrecognized in clinical practice and scarcely described in the literature. It is characterized by physical, cognitive, and psychological sequelae that affect the majority of survivors, with a negative impact on their quality of life and a significant increase in morbidity and mortality and healthcare costs.
Objective: the objective of this review is to synthesize recent knowledge and evidence available regarding post sepsis syndrome.
Method: a narrative review of articles published between 2000 and 2023 in PubMed, Sciencedirect, and LILACS was conducted. The MeSH terms "Sepsis," "Post ICU syndrome," and "Post sepsis syndrome" were used. A total of 221 articles were identified; 84 met inclusion criteria and were analyzed to describe the clinical and pathophysiological manifestations and impact of post sepsis syndrome.
Development: the available evidence shows that sepsis survivors present persistent impairment in physical, cognitive, and psychological domains. The syndrome is associated with prolonged immune dysfunction, frequent rehospitalizations, decreased functional autonomy, and increased cardiovascular and neuropsychiatric risk. High mortality rates up to five years after the event and high socioeconomic costs have also been documented. No standardized follow-up protocols or uniform rehabilitation strategies were identified in the reviewed literature.
Conclusions: post sepsis syndrome is an underestimated and underdiagnosed problem that represents a clinical and public health challenge. Large-scale studies are needed to define its true epidemiological burden and guide the implementation of multidisciplinary follow-up and rehabilitation programs to reduce its impact on patient survival and quality of life.

Keywords: Sepsis; Post ICU Syndrome; Post Sepsis Syndrome; Rehabilitation; Prognosis.

RESUMEN

Introducción: el síndrome post sepsis es una entidad emergente, poco reconocida en la práctica clínica, escasamente descrita en la literatura. Se caracteriza por secuelas físicas, cognitivas y psicológicas que afectan a la mayoría de los supervivientes, con impacto negativo en su calidad de vida y un aumento significativo de la morbimortalidad y de los costos en salud.

Objetivo: el objetivo de la presente revisión es sintetizar conocimientos y evidencia reciente disponible en torno al síndrome post sepsis.
Método: se realizó una revisión narrativa de artículos publicados entre 2000 y 2023 en PubMed, Sciencedirect y LILACS. Se emplearon los términos MeSH "Sepsis", "Post ICU syndrome" y "Post sepsis syndrome". Se identificaron 221 artículos, 84 cumplieron criterios de inclusión y fueron analizados para describir las manifestaciones clínicas, fisiopatológicas y el impacto del síndrome post sepsis.
Desarrollo: la evidencia disponible muestra que los supervivientes de sepsis presentan deterioro persistente en dominios físicos, cognitivos y psicológicos. El síndrome se asocia a disfunción inmunológica prolongada, rehospitalizaciones frecuentes, disminución de la autonomía funcional y aumento del riesgo cardiovascular y neuropsiquiátrico. Asimismo, se documentan elevadas tasas de mortalidad hasta cinco años después del evento y altos costos socioeconómicos. No se identificaron protocolos estandarizados de seguimiento ni estrategias de rehabilitación uniformes en la literatura revisada.
Conclusiones: el síndrome post sepsis es un problema infravalorado y subdiagnóstico que representa un desafío clínico y de salud pública. Se requieren estudios a gran escala que definan su verdadera carga epidemiológica y orienten la implementación de programas de seguimiento y rehabilitación multidisciplinaria para reducir su impacto en la supervivencia y la calidad de vida de los pacientes.

Palabras clave: Sepsis; Síndrome Post UCI; Síndrome Post Sepsis; Rehabilitación; Pronóstico.

INTRODUCTION

Sepsis is a heterogeneous clinical syndrome that affects more than 49 million people worldwide and causes approximately 11 million in-hospital deaths each year. Among survivors, mortality remains high; about 50 % die within the first year after discharge and up to 82 % within five years. It is estimated that about 75 % of survivors develop at least one new medical, psychological, or cognitive diagnosis after hospital discharge.[1]

Post-sepsis syndrome is a recently recognized condition characterized by persistent fatigue, neurocognitive alterations, and decreased functionality. Its pathophysiology involves immune dysregulation, chronic low-grade inflammation, oxidative stress, and mitochondrial dysfunction (figure 1).[1,2,3,4,5,6] It shares similarities with post-intensive care syndrome (PICS); in fact, 70 % of sepsis survivors suffer from PICS in the first three months after discharge from the ICU. It shares multiple characteristics with post-intensive care syndrome (PICS); in fact, about 70 % of sepsis survivors develop PICS within the first three months after discharge from the ICU. However, unlike PICS, post-sepsis syndrome can occur in patients treated outside of intensive care units. It is estimated that between 60 % and 70 % of those affected are unable to return to work even six years after hospital discharge. Although there is still no standardized definition, it is proposed that the term post-sepsis syndrome be used to refer to patients who develop persistent medical, psychological, or cognitive sequelae for weeks or months after overcoming the septic episode.[1]

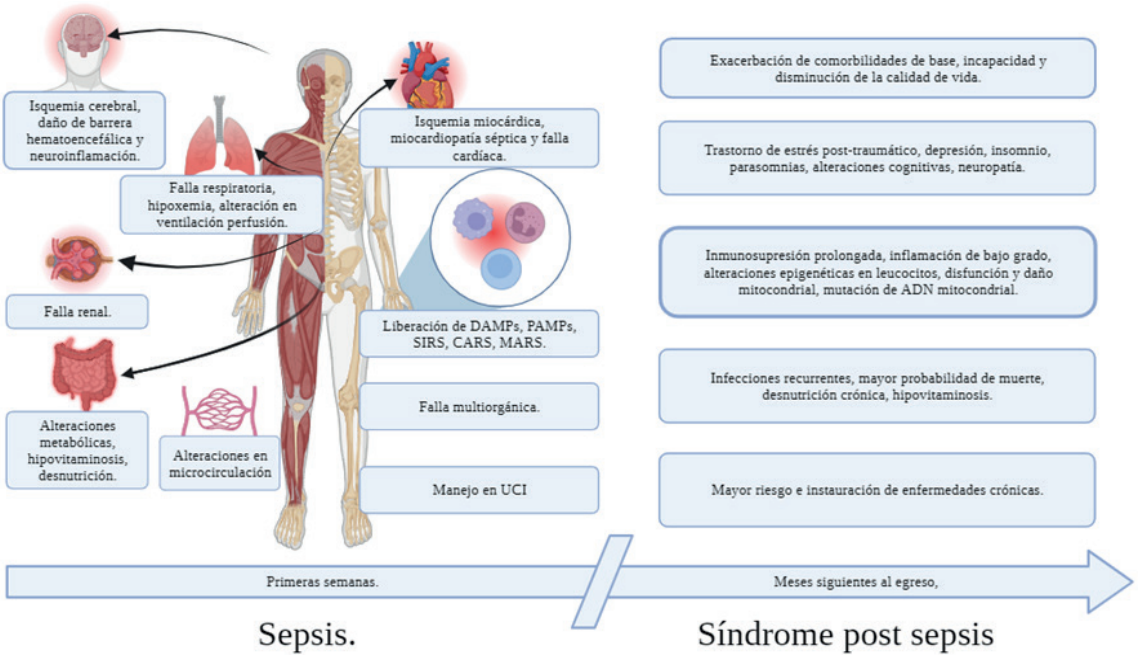

Figure 1. Conceptual model of post-sepsis syndrome

METHOD

A narrative review of the literature published between 2000 and 202 4 was conducted in the PubMed, ScienceDirect, and LILACS databases. The MeSH terms "Sepsis," "Post ICU Syndrome," and "Post Sepsis Syndrome" were used, identifying 221 articles. Of these, 7 were selected that addressed the clinical manifestations, pathophysiology, and implications of post-sepsis syndrome. Additionally, the authors incorporated 13 articles considered particularly relevant to the discussion.

DEVELOPMENT

History

For decades, sepsis was considered an acute disease, defined by a systemic inflammatory response to infection and focused on immediate hospital mortality. This approach, based on the so-called CHAOS theory, described sepsis as an abrupt process dominated by inflammatory imbalance and acute organ dysfunction. From this perspective, the primary therapeutic objective was to stabilize the patient and reverse shock.[1,2]

However, advances in critical care medicine and improvements in life support strategies have reduced in-hospital mortality, revealing that sepsis does not end with the resolution of the acute episode. Many surviving patients develop persistent complications, which has led to a rethinking of the conceptual paradigm of the disease. Within this new framework, post-sepsis syndrome has emerged, a recently recognized condition that manifests as fatigue, neurocognitive alterations, and decreased functionality. Its pathophysiology is associated with immune dysregulation, persistent inflammation, oxidative stress, and mitochondrial dysfunction (figure 1).[1,2,3,4,5,6]

This syndrome shares similarities with post-intensive care syndrome (PICS). In fact, it is estimated that about 70 % of sepsis survivors admitted to intensive care units will develop PICS within the first three months after discharge. However, unlike PICS, post-sepsis syndrome also affects patients treated outside the intensive care setting. Among those affected, 60 % are unable to return to work even six years after hospital discharge. Although there is still no universally accepted definition, it is proposed that the term post-sepsis syndrome should include patients who develop persistent medical, psychological, or cognitive sequelae for weeks or months after the resolution of the septic episode.[1]

Pathophysiology

Post-sepsis syndrome is a proinflammatory, immunocompromised state that perpetuates immune dysfunction (figure 2). This phenomenon is caused by epigenetic changes induced during the acute phase of sepsis, which permanently reprogram immune cells. Even during convalescence, DNA and histones remain methylated, leading to the repression of genes involved in TNF-α, IL-1β, IL-12, and CXCL-2/MIP2-α expression in antigen-presenting cells, as well as IFN-γ in CD4+ T lymphocytes.[5,6,7,8]

Murine models have shown that these repressive epigenetic modifications also affect hematopoietic progenitors in the bone marrow, leading to permanent metabolic reprogramming in innate immune system cells. These alterations occur mainly during the first month after the septic episode, a period in which macrophages acquire a dysfunctional phenotype.[9]

During sepsis, massive apoptosis of CD4+ and CD8+ T lymphocytes occurs,[10] with subsequent numerical recovery around six months after hospital discharge. However, these cells show reduced functionality; CD4+ T lymphocytes have limited immunological capacity, and CD8+ T lymphocytes exhibit lower antigenic sensitivity.[11] Consequently, sepsis survivors secrete lower levels of IFN-γ than healthy individuals[12] and have a predominant population of neutrophils and immature granulocytes.[13]

Likewise, persistent defects in the expression of Toll-like receptors and NF-κB, and in the signaling pathways of IL-4 and T and B lymphocyte receptors, have been identified and are associated with high mortality rates up to one year after discharge from the ICU.[14] This state of prolonged immunosuppression is also related to telomere shortening, premature cellular aging, intestinal barrier dysfunction, dysbiosis, DNA damage, and mitochondrial dysfunction.[15]

Epidemiology

The epidemiology of post-sepsis syndrome remains poorly understood. Many cases likely fall within the spectrum of post-intensive care syndrome (PICS), making it difficult to define precisely. In a study of 192 patients discharged from the ICU, 63,5 % of survivors had one or more alterations consistent with PICS. 32,3 % reported physical impairment, 14,6 % mental alterations, and 37,5 % cognitive impairment.[16]

Similarly, a prospective observational study evaluating the quality of life of 1,731 sepsis survivors showed that 47,8 % experienced a new episode of sepsis after discharge. All participants reported multisystemic symptoms—sensory, digestive, thoracic, renal, musculoskeletal, and integumentary—as well as psychological disorders such as anxiety, depression, fatigue, and sleep disturbances; 29,3 % expressed dissatisfaction with the medical care received after hospital discharge.[17]

Latin American studies report mortality rates up to 72 % one year after discharge.[18] Similarly, a prospective observational study reported a two-year mortality rate of 52 % in patients discharged from the ICU and a PICS frequency of 70 % at three months.[19] Grette et al.[15] described progressive mortality according to follow-up time: 9–41 % at 90 days, 9–66 % at one year, 8–70 % at two years, and 21–100 % at five years.

In terms of functionality, Montuclard et al.[20] noted that one-third of ICU survivors experience difficulties performing basic activities such as bathing, showering, or moving in bed. In Colombia, a study of 150 patients showed that an ICU stay longer than 48 hours was associated with an in-hospital mortality rate of 69 %.[21] Another study of 189 patients showed that 27 % of survivors had functional impairment and 8 % required daily assistance; in addition, a linear relationship was observed between the number of days spent in the ICU and mortality after discharge, stabilizing at around 35 % for prolonged stays.[22]

Patients who have suffered from sepsis have a two-year mortality rate of close to 70 %[23,24] and a higher risk of cognitive impairment compared to those hospitalized for other causes.[25] In economic terms, there are still no global estimates of the cost associated with post-sepsis syndrome, but the available figures illustrate its significant impact; in Brazil, the estimated cost per septic patient is $9 600;[26] [user8] [SM9] in Europe, it ranges from €23 000 to €29 000;[27] and in the United States, from $24 638 to $38 298 per patient.[28]

Mitigation of post-sepsis syndrome

Mitigation of post-sepsis syndrome begins at the time of hospitalization. At this stage, medical efforts should focus on reducing the long-term impact of sepsis through a multidisciplinary approach, given the syndrome's heterogeneity. Its management requires the coordinated participation of specialists in internal medicine, infectious diseases, critical care medicine, mental health, and rehabilitation.[29,30]

During the acute phase, early admission to the intensive care unit (ICU) is essential. The administration of antibiotics within the golden hour is associated with a significant reduction in mortality.[31] Likewise, controlling the source of infection, preventing organ failure, and implementing physiological support measures—such as avoiding hypoxemia and hyperoxia, performing response-directed fluid therapy, and using vasopressors early to optimize perfusion—are effective strategies that increase survival.[29,30,31]

Early nutritional support is another essential pillar of management, as it counteracts the metabolic losses of the hypercatabolic phase. This approach helps preserve glycogen and lipid reserves and slows the accelerated loss of muscle mass.[32,33] It is essential to determine individual caloric and protein requirements based on the patient's metabolic rate and energy requirements to avoid underestimating their needs. Therefore, nutritional goals should be individualized under the supervision of a nutrition specialist.[34]

Despite optimal metabolic therapy, many patients experience multiple organ failure, gastrointestinal dysfunction, and mitochondrial dysfunction, conditions that limit the anabolic response even with adequate nutrition.[35,36] Mitochondrial dysfunction, together with oxidative stress and apoptosis, profoundly alters cellular metabolism and contributes to genomic damage by releasing damage-associated molecular patterns (DAMPs), thereby increasing mortality.[37] In some patients, this mitochondrial damage is irreversible; therefore, mitochondrial renewal strategies have been proposed, such as antioxidant use, which could promote ATP production, increase mitochondrial biogenesis, and reduce the inflammatory response.[38,39] Among the experimental therapies, Mdivi-1 stands out as a mitochondrial fission inhibitor that improves membrane potential and ATP synthesis while decreasing reactive oxygen species (ROS) production. Its use has been associated with higher survival rates in preclinical models of sepsis.[39]

Sepsis combines simultaneous phases of hyperinflammation and immunosuppression, the latter persisting even after hospital discharge, which predisposes patients to recurrent episodes of sepsis and increases mortality from secondary infections.[40,41,42] This prolonged immunosuppression results from alterations in innate and adaptive immune responses and is a significant determinant of a poor long-term prognosis. Modulation of immune function has been proposed as a strategy to improve recovery in survivors. In this context, the heterogeneity of septic patients could justify the individualized use of immunoregulatory agents such as ascorbic acid, cobalamin, and retinoic acid, with potential benefits on the inflammatory response and immune homeostasis.[43,44]

Recurrence of sepsis

The medical community's priority should be preventing sepsis and closely monitoring survivors, ideally through infectious disease control and enrollment in post-ICU programs. These measures are highly recommended after surviving a septic episode. Comprehensive strategies have been proposed that include antibiotic stewardship programs, promotion of hand hygiene, routine vaccination, prevention of infections in hospital settings, adequate nutritional care, and public education.[44]

Among complementary preventive measures, the use of antioxidant agents has been suggested, although their efficacy is still under evaluation. Likewise, annual vaccination against SARS-CoV-2, pneumococcus, and Haemophilus influenzae represents a simple but effective intervention to reduce the risk of serious infections in sepsis survivors.[44,45,46] Awareness of sepsis and education of the general population are fundamental elements

in reducing its morbidity and mortality. The implementation of prevention strategies can reduce the incidence of post-sepsis syndrome. One study reported that only 32 % of people recognized the symptoms of sepsis, and only 17 % identified its risk factors.[47] The lack of consensus on the definition of sepsis could contribute to this low level of knowledge. In response, various international organizations have promoted global awareness campaigns, such as World Sepsis Day on September 13.[48] However, despite its high prevalence, the volume of internet searches on sepsis continues to be lower than that recorded for other critical illnesses, such as stroke or acute myocardial infarction.[49]

Physicians can play a decisive role through educational campaigns and the development of outreach materials on sepsis and post-sepsis syndrome.[50] A 2018 meta-analysis showed that implementing infection control programs, antimicrobial stewardship, and hand hygiene protocols can reduce the risk of hospital-acquired infections by up to 48 %.[51] Another meta-analysis showed that de-escalation antibiotic therapy and empirical prescribing guided by the site of infection significantly reduce mortality in hospitalized patients with infections.[52] Taken together, the evidence supports that healthcare professionals should adhere to current antimicrobial guidelines and prescribe antibiotics rationally and thoughtfully.[51,52]

An underdiagnosed condition

Post-sepsis syndrome is often an overlooked condition. Most survivors experience persistent fatigue during the first year after hospital discharge, which impairs their ability to concentrate and perform daily activities.[53,54] One in three patients fails to recover their baseline health status. Survivors often present with multisystem manifestations, including sensory, digestive, integumentary, cardiovascular, musculoskeletal, and renal disorders.[17] About 70 % of septic patients and 100 % of those with multiple organ failure develop critical illness polyneuropathy.[55] Strategies such as regular exercise, stress management, meditation, music therapy, and rest may help mitigate fatigue in these patients.[53,54,55]

Approximately one-third of sepsis survivors develop dysphagia, and 84 % do not regain normal swallowing function at the time of discharge.[56] Dysphagia increases the risk of aspiration, aspiration pneumonia, and malnutrition.[57] Predisposing factors include prolonged intubation and mechanical ventilation; therefore, otolaryngological evaluation of septic patients upon discharge from the ICU is recommended. Treatment options include modifications in diet texture, postural maneuvers, therapeutic exercises, nerve stimulation, and even proton pump inhibitors, sucralfate, or aluminum hydroxide.[58]

For more than five decades, musculoskeletal involvement has been recognized in sepsis survivors. On the seventh day of multiple organ failure, a significant reduction in the cross-sectional area of the rectus femoris muscle is observed, attributed to an imbalance between muscle protein synthesis and catabolism. Sarcopenia contributes to unfavorable clinical and functional outcomes. Patients survive with sustained catabolism, amplified by advanced age. Mitochondrial dysfunction, hypoperfusion, alterations in the neuromuscular junction, satellite cell damage, and protein loss are postulated to be the main determinants of long-term functional disability.[59,60,61,62,63,64,65,66]

Musculoskeletal compromise reflects alterations in satellite cells—responsible for myofibrillar regeneration—and mitochondria, which increase proteolysis, reduce protein synthesis, and promote the release of damage-associated molecular patterns (DAMPs). Satellite cells are essential for maintaining lean mass, and experimental studies show that their dysfunction persists until day 28, with transcriptomic changes in oxidative phosphorylation and mitochondrial biogenesis pathways, limiting muscle repair.[67] The LIFE study demonstrated that aerobic exercise is one of the most effective interventions for recovering muscle mass and physical function.[68] At the same time, cardiopulmonary rehabilitation is another key component for the recovery of critically ill patients. However, anabolic resistance and persistent inflammation may limit the response to treatment.[69]

Early mobilization in the ICU has shown variable results. Electrical stimulation of the limbs for five days attenuates muscle loss and proteolysis, although without a significant impact on strength.[70,71,72] The ExPrES study showed better preservation of muscle mass with a 14-day protocol combining electrical stimulation, protein supplementation, and rehabilitation exercises.[73]

Sepsis also has lasting cardiovascular repercussions. Septic cardiomyopathy or acute myocardial infarction may occur during the acute phase, and cardiovascular complications may persist for years, attributable to chronic inflammation, mitochondrial dysfunction, neurohumoral activation, endothelial dysfunction, and accelerated atherosclerosis.[74,75] Patients with a history of sepsis have a 1,65- to 1,77-fold increased risk of heart attack, stroke, heart failure, and death, and this increase persists for at least five years after the acute injury.[76]

Recent studies reinforce this association. Jentzer et al.[77], in a retrospective cohort of 808,673 patients, documented a 1,43-fold increase in hospitalizations for cardiovascular events. Angriman et al.[78], in a cohort of 254 241 survivors without previous cardiovascular disease, reported a 1,3-fold increase in the risk of cardiovascular death and stroke. Heart failure is the most frequent reason for admission in these patients. In addition, they are six times more likely to develop atrial fibrillation, which increases the risk of stroke by 1,22 to 1,91 times. However, the risk of bleeding usually makes anticoagulation during hospitalization inadvisable.[79,80]

Although the Surviving Sepsis campaign does not include specific recommendations for post-discharge cardiovascular follow-up, current evidence suggests that patients should adhere to early monitoring and comprehensive cardiovascular risk assessment programs, including consideration of body weight, renal function, cardiac function, blood pressure, heart rate, and body mass index. There is no substantial evidence on the use of beta-blockers and statins, or on the assessment of thrombotic and hemorrhagic risk in the context of post-sepsis syndrome, but their use may be prudent in selected cases.[31]

Sepsis also has a significant impact on neuropsychiatric function. Delirium is common during the acute phase and may precede sustained cognitive impairment. A marked reduction in cognitive function has been documented one year after discharge, with a 10 % increase in the incidence of moderate to severe impairment, persisting for up to eight years.[25] This phenomenon is attributed to neuroinflammation, alteration of the blood-brain barrier, glial activation, neurotransmitter dysfunction, and neuronal loss, which can cause irreversible damage.[81]

Post-sepsis syndrome is also associated with an increased risk of anxiety, depression, and post-traumatic stress disorder. Many survivors report distressing memories of their stay in the ICU. Despite the high prevalence of these sequelae, most do not receive adequate psychological care or social support, despite the potential benefits of cognitive-behavioral therapy and pharmacological treatments.[17]

Healthcare personnel must be aware of the magnitude and impact of post-sepsis syndrome. A retrospective study in the United States found an almost threefold increase in healthcare service use after a septic episode compared with the previous period. In addition, job abandonment reaches up to 70 %, with significant economic implications. Despite this reality, there are no evidence-based interventions that promote return to work or full recovery.[82]

In-person or telephone follow-up one month after discharge could have a positive impact on patient health. The measures described in this review could be the first step toward a personalized approach to post-sepsis syndrome (table 1).[17] Personalized medicine, supported by multidisciplinary teams and post-sepsis programs (figure 2), can improve recovery and reduce recurrence. Classifying patients into clinical phenotypes, as proposed by the SENECA study, using a combination of clinical variables and biomarkers, would enable the identification of subgroups at higher risk of morbidity and mortality and guide targeted interventions, such as targeted fluid therapy. Finally, multidisciplinary care and early screening with validated mental health tools can facilitate the timely detection of psychiatric disorders and optimize functional recovery.[83,84,85,86,87]

Table 1. Management of post-sepsis syndrome

Management of post-sepsis syndrome	
Early rehabilitation:	- Physical mobilization. - Physical therapy. - Occupational therapy.
Cognitive rehabilitation:	- Cognitive training: crossword puzzles, word searches, reading. - Neuropsychological rehabilitation. - Mindfulness. - Meditation.
Psychological support:	- Cognitive behavioral therapy - Stress reduction and mindfulness - EMDR (Eye Movement Desensitization and Reprocessing)
Multidisciplinary care:	- Multidisciplinary approach - Care coordination - Discharge planning - Post-sepsis program. - Follow-up by infectious disease specialists, internal medicine specialists, and critical care specialists.
Post-sepsis medical care:	- Cardiovascular risk management. - Medication review. - Vaccination. - Prophylactic antibiotics.
Education and self-management:	- Information about the condition. - Self-management strategies. - Hygiene.
Workplace accommodations:	- Workplace adjustments. - Modification of tasks. - Flexible schedules.
Early rehabilitation:	- Physical mobilization. - Physical therapy. - Occupational therapy.

Figure 2. Post-sepsis follow-up guidelines

CONCLUSIONS

Post-sepsis syndrome is an underestimated and underdiagnosed condition that severely affects the quality of life of survivors, who have high rates of physical and psychiatric morbidity, as well as a considerable economic impact on health systems. Following a septic episode, cellular pathophysiological alterations occur, leading to immunoparalysis and low-grade chronic inflammation, with consequences that are often irreversible. This syndrome worsens the prognosis and survival of patients discharged from the intensive care unit. Given the lack of large-scale research, it is recommended that studies be promoted to enable the early identification of patients who could benefit from personalized care after sepsis. It is necessary to understand the influence of different phenotypes on the evolution of post-sepsis syndrome to implement effective interventions at the right time to optimize recovery and reduce long-term sequelae.

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