Chapter 7

SEPSIS

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Sepsis is a physiological and biochemical dysfunction resulting from an infection, usually bacterial (Huang; Cai and Su, 2019; Hunt, 2024). Its complex pathogenesis involves immunological changes, autophagy, an unbalanced inflammatory response, coagulopathy, and neuroendocrine abnormalities (Huang; Cai and Su, 2019). Lack of early diagnosis and treatment can lead to septic shock, organ failure, and death (Karampela; Fragkou, 2022).

Although sepsis treatment has advanced, incidence and mortality continue to rise, with over 30 million cases annually worldwide, making it a leading cause of death in critically ill patients. Advances in treatment have reduced organ failure, but permanent immunological dysfunction has become the main cause of death in advanced sepsis (Huang; Cai and Su, 2019). The heterogeneity of patients, varying by etiology and severity, remains a challenge for sepsis management and diagnosis, with no reliable tests available in emergencies (Huang; Cai and Su, 2019; Hunt, 2024).

Sepsis affects 1-2% of hospitalized patients, with hospital mortality around 27%, increasing to 42% in intensive care units. Hospital-acquired infections account for up to a quarter of cases, with substantial economic costs, reaching about $23.6 billion in the US in 2013, with an annual growth rate of 11.5% (Huang; Cai and Su, 2019; László *et al.*, 2015).

Diagnostic criteria differ inside and outside the ICU. In the ICU, a SOFA score of 2 points in patients with infection suggests sepsis. Outside the ICU, the presence of two or more qSOFA criteria is used. Biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), TNF-α, IL-6, MCP-1, and miRNA are essential for early diagnosis (Karampela; Fragkou, 2022; Hunt, 2024). Sepsis involves dysfunctions in multiple organs, making clinical diagnosis challenging (Karampela; Fragkou, 2022; Hunt, 2024).

Treatment for sepsis includes antibiotics, antivirals, and vasoactive agents, although there are no FDA-approved specific therapies. Research focuses on modulating the inflammatory response, coagulopathy, and immunological dysfunction. In the early stages, excessive inflammatory response is critical, while in advanced sepsis, persistent immunological dysfunction predominates (László *et al.*, 2015; Hunt, 2024).

Biomarkers like PCT and CRP are widely used in sepsis diagnosis and treatment guidance but face challenges of sensitivity and specificity (Huang; Cai and Su, 2019). New alternatives, such as regulating the inflammatory response, are being explored. Corticosteroids, anti-cytokine agents, and kinase inhibitors can be used to suppress hyperinflammation in sepsis (Karampela; Fragkou, 2022).

Advances in bioinformatics and artificial intelligence show promising results in developing new diagnostic tools. Short-acting β-blockers and blood purification techniques have shown potential as complementary therapies. The SOFA score, which combines clinical signs and biomarkers of organ dysfunction, is an important diagnostic criterion (Karampela; Fragkou, 2022).

Classifying sepsis into distinct categories can facilitate the identification of more specific treatments. Sensitive and specific laboratory tests are needed to rapidly detect the onset and extent of the inflammatory response and monitor disease progression. However, the role of a well-trained and experienced physician remains irreplaceable (László *et al.*, 2015).

EPIDEMIOLOGY

Initiatives to improve the epidemiological understanding of sepsis are essential. For this, sepsis must be included in national research and healthcare agendas, with increased resources for research and programs (Cassini *et al.*, 2021). According to the Global Burden of Sepsis study, 31.5% of sepsis survivors who previously did not require care now present this need, increasing the life risk for such patients. Mortality within 12 months after discharge was 30.7% (Fleischmann-Struzek and Rudd, 2023). The global burden of sepsis in 2020 was estimated at 48.9 million incident cases, with a rate of 677.5 cases per 100,000 inhabitants. However, despite the increase in studies on sepsis incidence, calculating this measure at a global level remains a challenge (Fleischmann-Struzek and Rudd, 2023).

The mortality rate of sepsis and septic shock ranges between 30% and 50%, depending on factors such as race, gender, age, and organ impairment. Male, elderly, and immunocompromised patients are more likely to develop these conditions. In children, sepsis may be linked to genetic inheritance (Pandey, 2024).

The incidence of sepsis and septic shock grows by 9% annually (Martin *et al.*, 2003). The anatomical site of infection significantly impacts the sepsis mortality rate. Lower respiratory and biliary tract infections and intra-abdominal infections are associated with higher lethality, while skin and musculoskeletal infections show lower mortality rates. Lower respiratory tract infection was the leading cause of death, followed by genitourinary tract infections and systemic fungal infections. The incidence of these infections has shown a sharp increase, especially musculoskeletal and skin infections (Chou *et al.*, 2020).

Higher prevalence and hospital mortality rates are observed in low- and middle-income countries (LMICs). Maternal sepsis is one of the leading causes of sepsis incidence and mortality globally. During the COVID-19 pandemic, the incidence of non-virus-related sepsis decreased due to the reduction in other respiratory infections and post-surgical sepsis. Interventions such as pneumococcal pneumonia vaccination and ventilator-associated bundles have been used to prevent infections. Assessing the impact of the infection site is crucial for better treatment. Hospital mortality is higher in patients with intra-abdominal infection and lower in cases of primary bacteremia (Pandey, 2024).

Risk factors for sepsis include diabetes, malignancy, chronic kidney and liver disease, corticosteroid use, burns, major surgery, trauma, permanent catheters, prolonged hospitalization, hemodialysis, and extremes of age. Nutritional assessment is relevant, with critically ill patients needing 25 to 30 kg to meet protein needs (Huang et al.). Markers such as SDMA (Symmetrical Dimethylarginine) and ADMA (Asymmetrical Dimethylarginine) are high-risk combinations for sepsis survival (Winkler *et al.*, 2024). Furthermore, studies show that pre-existing comorbidities increase the risk of adverse outcomes after sepsis, highlighting the importance of recognizing these high-risk populations (age, underlying diseases, and vulnerable groups) (Pandey, 2024).

DIAGNOSIS

Sepsis triggers a systemic inflammatory response that can lead to multiple organ failure. Early signs include fever, tachycardia, tachypnea, and leukopenia. Severe sepsis could be indicated by hypoxia, hypotension, cyanosis, brain dysfunction, oliguria, and paralytic ileus and may progress to septic shock (Pandey, 2024). The most accepted definition by the 45th Critical Care Medicine Society defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection. The qSOFA and SOFA scores are used for assessment, with a positive diagnosis for sepsis if the qSOFA is greater than two points or the SOFA reaches two points. However, these scores are criticized for low specificity and the possibility of delaying the diagnosis and treatment of severe infections (Pant; Mackraj and Govender, 2021).

The early diagnosis of sepsis is crucial for patient prognosis and reducing mortality, typically achieved through blood cultures and molecular tests. However, it is hindered by the absence of well-established signs and symptoms, and the lack of a technical standard that unanimously confirms the diagnosis (Pant; Mackraj and Govender, 2021). Early identification of the worsening condition and the genesis of the infection is essential. Unfortunately, conventional indicators like fever and leukocytosis, as well as new biomarkers, are not sufficiently sensitive or specific to cover the variability of the pathobiology of different patients. Thus, it is unlikely that a single diagnostic parameter will be sufficient; using multiple tests is more reliable (Molnár *et al.*, 2016).

The lack of a rapid and precise test for the identification of sepsis complicates the correct diagnosis, often challenging healthcare professionals. This can result in overtreatment with antibiotics «just-in-case,» inadequate or delayed diagnoses, and failure to recognize non-infectious conditions. Sepsis-3 attempts to standardize terminology to avoid the inappropriate use of terms, as not every infection results in sepsis (Tidswell; Inada-Kim and Singer, 2021). A retrospective review of 369 patients with suspected infection revealed that only 22% met the sepsis criteria after independent evaluation, highlighting inconsistencies in current diagnoses and coding (Tidswell; Inada-Kim and Singer, 2021). This inconsistency compromises the accurate epidemiology of sepsis, making it difficult to understand the extent of the problem and evaluate new treatment and diagnostic strategies. Applying levels of certainty to the diagnosis is recommended to increase the accuracy of records and improve clinical care (Tidswell; Inada-Kim and Singer, 2021).

The microbiological diagnosis of sepsis is often carried out by blood culture, preferably before starting antibiotic treatment, with the collection of 2 to 3 sets to identify the origin and etiological agent of the infection. This process requires optimization of the pre-analytical, analytical, and post-analytical stages (Escartín; Martínez-López and Nadal-Barón, 2023). Although standard blood culture techniques are excellent for identifying and isolating microorganisms, they have disadvantages such as long response times, which can

take up to 5 days for pathogen growth, plus an additional 48 hours for antibiotic susceptibility testing. Furthermore, they have low sensitivity, requiring a large sample volume, with up to 63% of cases potentially resulting in false negatives after treatment initiation, and are subject to pre-analytical variables (Lippi, 2019).

Pre-analytical measures include proper sample collection, encompassing skin sterilization, blood volume collected, number of samples, incubation time of the bottles, and transport to the laboratory, all crucial factors for diagnostic time and quality (Escartí; Martínez-López and Nadal-Barón, 2023). In addition to blood cultures, some hospitals adopt standards for requesting laboratory tests, including complete blood count, basic biochemistry, coagulation study, acid-base balance, urine, and biomarkers, which generate alerts for rapid control of samples. Analytical processes involve the rapid processing of bottles flagged as positive and the use of rapid identification and antimicrobial susceptibility testing methods, including molecular diagnostics, rapid diagnostics, and gram tests, important for detecting microorganisms and resistance genes in 30 minutes to 5 hours (Escartín; Martínez-López and Nadal-Barón, 2023).

The T2 magnetic resonance technique stands out, using paramagnetic nanoparticle sensors to detect bacteria and yeast in the blood with high sensitivity (>95%) and low cell concentration (1 cell/ml), though it faces interpretation challenges compared to traditional tests (Escartín; Martínez-López and Nadal-Barón, 2023). Rapid methods monitor bacterial growth in response to antibiotics using techniques like nephelometry, PNA FISH with morphokinetic cell analysis, microfluidics with fluorescence microscopy, microscopy imaging, volatile emission matrix detection, and flow cytometry (Escartín; Martínez-López and Nadal-Barón, 2023).

Post-analytical actions depend on joint medical, hospital, and laboratory evaluation, analyzing the patient›s clinical context, test results, and necessary therapeutic measures (Escartín; Martínez-López and Nadal-Barón, 2023). Various screening tools, such as early warning signs and the Rothman Index, are used to rapidly detect sepsis, even in the pre-hospital phase. The Surviving Sepsis Campaign (SSC) lists screening and diagnostic tools, considering clinical parameters such as heart rate, respiratory rate, temperature, blood pressure, oxygen saturation, lactate, urea, C-reactive protein, complete blood count, blood cultures, urine cultures, and cultures of other body fluids. Imaging techniques are also useful for confirming the condition (Pandey, 2024).

Given the various diagnostic difficulties, several scoring systems have been developed to assess sepsis severity and predict outcomes. Initially, the definition of sepsis depended on the Systemic Inflammatory Response Syndrome (SIRS) criteria. However, this approach was questioned for its lack of clinical specificity. Currently, the definition of sepsis is based on the objective presence of acute dysfunction indicating an inadequate host response to infection. The evolution of risk stratification strategies offers better opportunities for early detection of sepsis (Laura *et al.*, 2020).

Alerts are essential components of systems designed to draw healthcare professionals› attention to critical information when certain parameters are exceeded. These help in continuous monitoring of changes in the patient›s condition, facilitating timely interventions. However, the dispersion of information can hinder the detection of changes and result in ineffective care. With technological advancement, machine learning (ML) algorithms have been developed to improve early diagnosis and management of sepsis, even with established institutional protocols. ML enables computers to learn and act autonomously, offering accurate predictions (Schubel et al., 2020). A collaboration between Laura® and researchers from the Federal University of Paraná (UFPR) resulted in Robot Laura®, which uses AI and ML to reduce sepsis deaths through early identification. This technology integrates data systems to collect information, perform statistical calculations, and provide conclusions about the presence of conditions favorable to sepsis. The study aimed to investigate the impact of these algorithms on healthcare professionals› decision-making and demonstrate how technology can contribute to nursing practice in sepsis patients (Schubel *et al.*, 2020).

Various ML algorithms are used for the diagnosis, prognosis, and phenotyping of sepsis. Supervised algorithms develop sepsis predictions, while unsupervised ones highlight underlying structures and hidden patterns. Supervised learning predominates in most diagnostic and prognostic applications, while unsupervised learning defines phenotypes, facilitating the use of specific therapies and the selection of patients for clinical trials (Komorowski *et al.*, 2022).

The COMPOSER model (COnformal Multidimensional Prediction Of SEpsis Risk) aims to predict the risk of sepsis early, minimizing false alarms (Komorowski et al., 2022). ML techniques reveal metabolic disturbances in sepsis, helping to distinguish between pathological conditions and predict different therapeutic responses (Komorowski *et al.*, 2022). Biomarkers and post-translational modifications (PTMs) during infections and immune responses are essential for the diagnosis and treatment of sepsis (Chang; Li, 2022).

In addition to technological advances, the discovery and evaluation of sepsis biomarkers have the potential to improve diagnostic accuracy, indicate physiological pathways, guide clinical trials, and optimize clinical management (Komorowski *et al.*, 2022). A wide variety of biomarkers have been identified, including PRMs, chemokines, cytokines, DAMPs, non-coding RNAs, microRNAs, cell membrane receptors, metabolites, cellular proteins, soluble receptors, and complement system components. The review focused on the application of the models (diagnostic, prognostic, or phenotyping) and the nature of the input data, whether routine (clinical and laboratory) or non-routine (gene expression, cytokines, metabolomics, among others) (Komorowski *et al.*, 2022).

Biomarkers such as procalcitonin, C-reactive protein, and inflammatory cytokines are used for sepsis diagnosis and prognosis (Huang; Cai and Su, 2019). Nanotechnology and biosensors also show promise for overcoming diagnostic challenges, offering greater sensitivity and specificity (Pant; Mackraj and Govender, 2021).

Transcriptomics aims to improve the precision of sepsis diagnosis by providing better information about infection severity and prognosis compared to current biomarkers. This approach offers a broader evaluation of the body›s response to infection through the analysis of the host immune gene expression profile (mRNA). The test known as SeptiCyte Lab is already being marketed (Immunexpress, Seattle, WA), and a version of the test that takes 4 to 6 hours has received FDA authorization to aid in differentiating sepsis positive from systemic infection negative in patients suspected of sepsis admitted to the ICU on the first day. In a study involving ICU patients, the SeptiCyte Lab showed significantly higher diagnostic accuracy in differentiating between sepsis and SIRS compared to PCT. Studies suggest that transcriptomics-based tests may outperform biomarkers. Another relevant aspect of transcriptomics study is distinguishing between bacterial and viral infections and its use in sepsis risk stratification (Gunsolus *et al.*, 2019).

Studies that analyzed the transcriptome identified several modules related to sepsis (GSE185263 and GSE65682), along with others such as M2, M33, M35, M57, and M63. For instance, M33 was upregulated in severe sepsis, septic shock, and sepsis death compared to SIRS. The study also reports that these modules can differentiate the infectious focus of bacterial pneumonia, influenza pneumonia, mixed bacterial and influenza pneumonia, and non-infectious SIRS (Li *et al.*, 2023).

Combining advanced techniques with different types of omics data, such as genomics, proteomics, transcriptomics, and metabolomics, has shown significant advances in sepsis research. Algorithms like Support Vector Machines (SVM), Random Forests, and Stabl have proven effective in discovering new biomarkers and immunological profiles, being crucial for early disease identification and the development of personalized therapeutic strategies. A good example is the NAVOY algorithm, which can predict sepsis in real-time, using four hours of collected laboratory values and clinical parameters to identify patients at risk of developing sepsis three hours before its onset (Santacroce *et al.*, 2024).

Advancements include the deacetylation of the p53 protein, which promotes autophagy in renal cells, and the identification of peptidylarginine deiminase 2 (PAD2) as a promising biomarker. Other important biomarkers are CitH3 and GPR174, which indicate sepsis severity and prognosis (Chang; Li, 2022). The discovery of biomarkers related to infection, inflammation, immune imbalance, and organ dysfunction is crucial for clinical diagnosis, monitoring, and therapeutic intervention. Biomarkers such as procalcitonin, C-reactive protein, and inflammatory cytokines play an important role in early diagnosis and prognosis of sepsis (Huang; Cai and Su, 2019).

The use of biological markers may never overcome the diagnostic and prognostic difficulties in sepsis due to the fact that the condition does not present a single clear pathophysiology but rather a varied set of severe inflammatory responses to infection. Therefore, a single elevated marker during a simple infection as well as in a critical non-infectious disease cannot reliably provide information about the presence of infection or

disease severity, requiring the association and analysis of various biomarkers (Gunsolus *et al.*, 2019).

Nanotechnology, with electrochemical, optical, magnetic sensors, and immunosensors, offers greater diagnostic sensitivity and specificity. Electrochemical biosensors and immunosensors allow the detection of various biomarkers with high precision (Pant; Mackraj and Govender, 2021). Systems biology approaches, such as transcriptomics, proteomics, and metabolomics, are expected to contribute to a better understanding of sepsis and the development of new biomarkers and diagnostic tools (Reinhart et al., 2012). The integration of advanced technologies and clinical information can improve diagnostic accuracy and timeliness, suggest therapeutic targets, and optimize clinical management (Komorowski *et al.*, 2022).

The evolution of diagnostic technologies and the use of ML offer new perspectives for the detection and treatment of sepsis. Collaboration between healthcare professionals and technology is fundamental to developing innovative solutions that improve patient outcomes (Komorowski *et al.*, 2022).

TREATMENT

Due to the high mortality rates associated with sepsis, it is essential to implement effective treatment and management strategies to ensure patient survival. Implementing promising therapeutic options that consider the severity of the condition can reduce mortality and increase patient survival. The need to offer personalized treatment presents a challenge due to the diverse clinical manifestations of the pathology. Therapeutic approaches include implementing an aggressive resuscitation plan, antimicrobial treatment, and, in some cases, steroid administration (Mirijello; Tosoni, 2020). The heterogeneous occurrence of the disease and its impact on various systems complicate the formulation of a uniform treatment plan (Purcarea; Sovaila, 2020).

Early detection of sepsis is crucial for increasing survival rates, and new diagnostic tools are being developed to diagnose the disease and enable immediate treatments (Mirijello; Tosoni, 2020). Transcriptome analysis and the identification of prognostic markers are essential for developing diagnostic biomarkers and empowering personalized therapy (Hunt, 2024). Extensive studies have revealed inflammatory imbalances, immune dysregulation, mitochondrial damage, and coagulation disorders. The development of the use of nanoparticles as adjuvants or antibiotic therapy has shown promising results in treating sepsis (Escartín; Martínez-López and Nadal-Barón, 2023). Omics technologies and artificial intelligence are revolutionizing the approach to sepsis, providing detailed profiles, identifying biomarkers, and selecting specific therapeutic agents (Tindal *et al.*, 2021).

Using these tools has the potential to improve clinical outcomes, considering the variability of sepsis among individuals and tailoring the therapeutic approach as needed.

Sympathetic treatment lines, studies with micronutrients, and antioxidant and anti-inflammatory therapies show promise, although further studies are necessary to confirm their efficacy and safety. Biomarkers such as leukocytosis, procalcitonin, CRP, lactate, interleukins, adrenomedullin, and presepsin have played crucial roles in diagnosing and monitoring sepsis treatment response, but no single biomarker is sufficiently reliable (Huang; Cai and Su, 2019). Combining data from different biomarkers can help make more accurate diagnoses and facilitate monitoring of the treatment response (Mirijello; Tosoni, 2021).

Current treatment options include aggressive resuscitation, antimicrobial medications, and eventually, steroid administration. However, the etiological diversity and the variety of systems affected during a septic response present significant difficulties for adequate treatment (Tindal *et al*., 2021). Fluid administration is a cornerstone in managing hemodynamic instability, but optimizing this administration remains a challenge. Administering fluids in boluses can reduce arterial elastance, leading to vasodilation and a hyperdynamic state, while excessive administration is associated with organ dysfunction and death. To avoid delays in hemodynamic stabilization, early initiation of a vasopressor is recommended, although most vasopressors lack information on safe and effective doses. Antibiotic therapy is fundamental in treating sepsis, but inadequate therapy within the first 24 hours leads to eight times higher hospital mortality (Pant; Mackraj and Govender, 2021).

Moreover, some authors argue that the timing of interventions has an extreme impact on patient mortality. Thus, the 3-hour and 6-hour sepsis bundles should be replaced by a «1-hour bundle» with rapidly administered antibiotics and vasopressors. However, others believe this may lead to an undesirable increase in the use of antibiotics and vasopressors without solid evidence supporting this practice. The arbitrary «1-hour bundle» is not yet ready for real-world use, but early active resuscitation actions and protocolized follow-up are highly recommended. If there is no response to initial measures or if lactate levels remain elevated, immediate actions are necessary. Crystalloid solutions and antimicrobials are the foundation of therapy (Purcarea; Sovaila, 2020).

Despite the use of supportive therapy and adequate administration, antibiotics are often inefficient and have little effect on reducing the mortality rate from sepsis. Patients with sepsis-associated immune paralysis are susceptible to secondary infections, including invasive infections caused by multidrug-resistant (MDR) bacteria. Thus, these patients require specific strategies aimed at restoring immune function, in addition to antibiotic therapy and conventional treatments. These adjunctive therapies can help the immune system, prevent immune paralysis, and attenuate inflammatory responses (Pant; Mackraj and Govender, 2021).

Currently, new studies are focusing on improving biomarkers and gene expression for the early and specific detection of sepsis complications, promoting more adequate and individualized treatment. Another trend is the increasing inclusion of artificial intelligence resources for early detection and constant surveillance, aiming to improve identification

and action in the early stages. Nanotechnology has been prominent in combating infections caused by microorganisms, including those by resistant pathogens, revolutionizing the antimicrobial field. The use of nanotechnology-based biosensors represents a new strategy for the more sensitive diagnosis of sepsis-related biomarkers. These biomarkers are commonly evaluated for different purposes in the treatment of sepsis, such as diagnosis, prognosis, control, replacement, and stratification. Clinical detection of sepsis has been successful with the use of a small set of biomarkers, such as CRP, PCT, and interleukin-6 (IL-6) (Pant; Mackraj and Govender, 2021).

Biomarkers play a crucial role in the early detection of sepsis and risk classification, influencing therapeutic management, antibiotic administration, severity prediction, and evaluation of efficacy. Currently, more than 170 biomarkers have been discovered for the diagnosis of sepsis, highlighting PCT, CRP, IL-6, MCP-1, miRNA, among others (Huang, Cai & Su, 2019). CRP levels before treatment, obtained within a 48-hour interval, can be useful in assessing the response of patients with sepsis to antimicrobial therapy. Additionally, CRP at admission can be an important indicator of early infection and help in prognosis and treatment monitoring (Huang; Cai and Su, 2019). Elevated CRP levels can significantly correlate with infection severity, aiding in early diagnosis and prognosis in patients with sepsis (Pant; Mackraj and Govender, 2021). However, various non-infectious conditions can cause elevated CRP, resulting in low specificity for infections (Gunsolus *et al.*, 2019).

Procalcitonin (PCT) can be useful as a prognostic indicator in patients with sepsis. Although a single PCT value at the onset of the clinical condition is not very useful in predicting the patient›s outcome, several studies show that sequential measurement of PCT can help in assessing mortality risk. Additionally, it has been analyzed that the lack of a decrease or even an increase in its predictive value is associated with an unfavorable prognosis. Studies on patients with acute respiratory infections, including sepsis and septic shock, indicated that PCT-guided therapy resulted in lower antibiotic consumption, fewer side effects, and a lower fatality rate (Gunsolus *et al.*, 2019; Ehler; Busjahn and Schürholz, 2021).

Recent research has also revealed that microRNAs (miR-25) demonstrated higher diagnostic accuracy compared to previously mentioned markers, such as CRP and PCT. Moreover, the miRNA biomarker was able to distinguish between bacterial and viral causes of acute respiratory failure (Ehler; Busjahn and Schürholz, 2021).

Human studies have pointed to the relationship between persistent neutrophil dysfunction and increased risk of hospital infections, considering CD64 neutrophil (nCD64) a reliable marker to identify systemic infection, sepsis, and tissue injury with high sensitivity and specificity. According to research, patients exhibiting greater neutrophil dysfunction after sepsis are more likely to develop complications during ICU hospitalization. Despite producing low levels of cytokines, these neutrophils increase IL-10 production during sepsis, hindering T lymphocyte proliferation (Santacroce *et al.*, 2024). Evaluating interleukins, IL-6

is reduced in the first week of infection in survivors but increases in non-survivors. Thus, measuring IL-6 in neonatal sepsis diagnosis has proven to be an effective, non-invasive, and rapid method for early diagnosis (Huang; Cai and Su, 2019).

Analyzing presepsin (sCD14-ST) shows a significant increase within 2 hours of infection onset, peaking at 3 hours. Therefore, this biomarker currently holds potential for diagnosing adult sepsis, with several studies demonstrating that presepsin surpasses PCT, CRP, and IL-6 in terms of sensitivity and specificity in sepsis diagnosis. It can also effectively assess disease severity and prognosis (Huang; Cai and Su, 2019).

Currently, no specific and effective therapeutic drugs are available. The focus of drug development is on regulating inflammatory response, coagulation, and immune dysfunction, aiming to restore the body›s pro- and anti-inflammatory balance and improve patient prognosis. With advancements in sepsis treatment, there has been a significant reduction in the number of patients with multiple organ failure in the ICU. Persistent immune dysfunction is now the main cause of death in patients with advanced sepsis, making it the primary focus of medicinal treatment research. Some studies have evaluated immune responses in sepsis through the administration of TNF-α neutralizing antibodies, noting that two of these antibodies, Afelimomab and CytoFab, showed promise after some trials (Huang; Cai and Su, 2019).

Polymyxin B has antibacterial activity against Gram-negative bacteria and can bind and neutralize endotoxins that play a critical role in sepsis. A hemoperfusion system called polymyxin B (PMX-HP) was developed to remove endotoxins using polymyxin B as an adsorbent. Several studies have demonstrated the clinical efficacy of PMX-HP in patients with severe sepsis and septic shock, associating it with reduced mortality, improved hemodynamics, and increased pulmonary oxygenation in patients with septic shock (Huang; Cai and Su, 2019).

The administration of recombinant human soluble thrombomodulin (rhTM) for the treatment of disseminated intravascular coagulation (DIC) has been used in Japan for over a decade, showing promising results with a significant reduction in mortality (Huang; Cai and Su, 2019). Indeed, rhTM has proven effective in treating DIC, with phase III clinical studies demonstrating it to be more efficient than heparin in resolving the condition and ensuring patient safety. Some studies have shown that administering rhTM to septic patients significantly improved organ dysfunction according to Sequential Organ Failure Assessment (SOFA) scores and reduced mortality (Tindal *et al*., 2021).

Regarding the immune dysfunction that occurs in septic patients, some studies have demonstrated that the use of PD-1, a negative costimulatory molecule, can reverse immunosuppression by decreasing apoptosis levels, stimulating the cytokine profile in an anti-inflammatory direction, and increasing the production of IFN-γ and IL-2. According to these studies, employing coinhibitory molecules can shift a hyper-inflammatory response to a hypoactive response, which is crucial to reducing the risk of secondary infections and mortality. Thus, this therapeutic approach emerges as one of the most promising in sepsis treatment in the coming years (Huang; Cai and Su, 2019; Tindal *et al*., 2021).

The use of nanotechnology in antimicrobial treatment is being termed the «post-antibiotic era» due to the evolution of drug-resistant pathogens and the scarcity of new antibiotic research. Incorporating nanotechnology into antimicrobial drugs offers additional benefits beyond structural characteristics, such as overcoming resistance. For example, studies have shown that administering vancomycin through the CARG drug nanosystem was about ten times more effective than the free drug. Moreover, nanoparticle formulations can prolong the antibiotic›s lifespan, act as a gradual release system, reduce administration frequency, and improve therapeutic efficacy (Pant; Mackraj and Govender, 2021).

Transcriptome studies are also aiding in the analysis of candidate drugs for sepsis treatment. Some modules related to positive disease outcomes were enriched with phytoestrogen and ibuprofen genes. Other modules with negative outcomes were enriched with testosterone, urea, and vitamin B genes. These data can generate new hypotheses for potential medications as treatment options for sepsis (Li *et al.*, 2023).

Several studies have shown the benefits of using antioxidants, notably vitamin C, vitamin E, N-acetylcysteine, and melatonin, with results indicating that antioxidant therapy combined with standard therapy can reduce multiple organ failure, oxidative stress, and inflammation in patients with septic shock (Mirijello; Tosoni, 2021).

Melatonin is particularly interesting due to its protective effect, which includes inhibiting the activation of the NF-κB and NLRP3 inflammasome. The therapeutic approach using melatonin-loaded nanocarriers prevents its capture by macrophages, resulting in a prolonged circulation time. Additionally, this drug delivery system allows for on-demand delivery and targeted release at specific sites in response to the particular microenvironment rather than systemic administration of melatonin. This enables drug delivery to a specific location, relieving hepatic flow, which is often affected by sepsis (Pant; Mackraj and Govender, 2021).

Another recent research focus is the approach to gut microbiota, as the importance of the host flora in altering the immune response during sepsis has been emphasized, showing the predominance of certain bacterial communities after infection and apparently influencing the host›s reaction. Studies reveal that using prebiotics, probiotics, or symbiotics, and fecal transplantation could alter the microbiome, impacting clinical outcomes related to sepsis by acting as primary prevention, reducing the severity of the condition, and preventing secondary infections (Tindal *et al.*, 2021).

REFERENCES

CASSINI, Alessandro et al. Future directions and priorities in sepsis epidemiology research: a call for action. **Bulletin of the World Health Organization**, v. 99, n. 5, p. 398, 2021.

CHANG, Panpan; LI, Yongqing. Targeting Protein Post-Translational Modifications (PTMs) for Diagnosis and Treatment of Sepsis. **Frontiers in Immunology**, v. 13, p. 856146, 2022.

CHOU, Eric H. et al. Incidence, trends, and outcomes of infection sites among hospitalizations of sepsis: A nationwide study. **PloS one**, v. 15, n. 1, p. e0227752, 2020.

Ehler, J., Busjahn, C. & Schürholz, T. Which biomarkers are used to diagnose and control anti-infective therapy in sepsis?. **Anaesthesist** 71, 3–11 (2022).

ESCARTÍN, Maria Nieves Larrosa; MARTÍNEZ-LÓPEZ, Miguel Ángel; NADAL-BARÓN, Patricia. The microbiology of sepsis is more than the application of new technologies in diagnosis. **Revista Española de Quimioterapia**, v. 36, n. Suppl 1, p. 5, 2023.

FLEISCHMANN-STRUZEK, Carolin; RUDD, Kristina. Challenges of assessing the burden of sepsis. **Medizinische Klinik-Intensivmedizin und Notfallmedizin**, v. 118, n. Suppl 2, p. 68-74, 2023.

GUNSOLUS, Ian L. et al. Diagnosing and managing sepsis by probing the host response to infection: advances, opportunities, and challenges. **Journal of clinical microbiology**, v. 57, n. 7, p. 10.1128/jcm. 00425-19, 2019.

HUANG, Min; CAI, Shaoli; SU, Jingqian. The pathogenesis of sepsis and potential therapeutic targets. **International journal of molecular sciences**, v. 20, n. 21, p. 5376, 2019.

HUNT, Anne. Sepsis: an overview of the signs, symptoms, diagnosis, treatment and pathophysiology. **Emergency Nurse**, v. 32, n. 1, 2024.

KARAMPELA, Irene; FRAGKOU, Paraskevi C. Future perspectives in the diagnosis and treatment of sepsis and septic shock. **Medicina**, v. 58, n. 7, p. 844, 2022.

KOMOROWSKI, Matthieu et al. Sepsis biomarkers and diagnostic tools with a focus on machine learning. **EBioMedicine**, v. 86, 2022.

LÁSZLÓ, Ildikó et al. Sepsis: from pathophysiology to individualized patient care. **Journal of immunology research**, v. 2015, 2015.

LI, Qingsheng et al. A gene network database for the identification of key genes for diagnosis, prognosis, and treatment in sepsis. **Scientific Reports**, v. 13, n. 1, p. 21815, 2023.

LIPPI, Giuseppe. Sepsis biomarkers: past, present and future. **Clinical Chemistry and Laboratory Medicine (CCLM)**, v. 57, n. 9, p. 1281-1283, 2019.

MIRIJELLO, Antonio; TOSONI, Alberto. Sepsis: New Challenges and Future Perspectives for an Evolving Disease—Precision Medicine Is the Way!. **Medicina**, v. 57, n. 10, p. 1109, 2021.

MIRIJELLO, Antonio; TOSONI, Alberto; INTERNAL MEDICINE SEPSIS STUDY GROUP. New strategies for treatment of sepsis. **Medicina**, v. 56, n. 10, p. 527, 2020.

MOLNÁR, Zsolt et al. Sepsis: diagnostic and therapeutic challenges. **BioMed research international**, v. 2016, 2016.

PANDEY, Swarnima. Sepsis, Management & Advances in Metabolomics. **Nanotheranostics**, v. 8, n. 3, p. 270, 2024.

PANT, Amit; MACKRAJ, Irene; GOVENDER, Thirumala. Advances in sepsis diagnosis and management: a paradigm shift towards nanotechnology. **Journal of Biomedical Science**, v. 28, p. 1-30, 2021

PURCAREA, Adrian; SOVAILA, Silvia. Sepsis, a 2020 review for the internist. **Romanian Journal of Internal Medicine**, v. 58, n. 3, p. 129-137, 2020.

REINHART, Konrad et al. New approaches to sepsis: molecular diagnostics and biomarkers. **Clinical microbiology reviews**, v. 25, n. 4, p. 609-634, 2012.

SANTACROCE, Elena et al. Advances and Challenges in Sepsis Management: Modern Tools and Future Directions. **Cells**, v. 13, n. 5, p. 439, 2024.

SCHUBEL, Laura et al. Informatics and interaction: applying human factors principles to optimize the design of clinical decision support for sepsis. **Health informatics journal**, v. 26, n. 1, p. 642-651, 2020.

TIDSWELL, Robert; INADA-KIM, Matt; SINGER, Mervyn. Sepsis: the importance of an accurate final diagnosis. **The Lancet Respiratory Medicine**, v. 9, n. 1, p. 17-18, 2021.

TINDAL, Elizabeth W. et al. Emerging therapeutic targets for sepsis. **Expert opinion on therapeutic targets**, v. 25, n. 3, p. 175-189, 2021.