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# *Sepsis – treatment in the first hours*

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## Abstract

Sepsis is a multi-organ failure in which the body is unable to mount an appropriate response to an ongoing infection, making those with weakened immune systems more susceptible to its development. It can impact people across all age groups and is a common cause of emergency hospital admissions that has a high mortality rate. Its etiology may be bacterial, viral, or fungal. Due to the broad spectrum of potential pathogens, diagnosis is complex and often not definitive, meanwhile it should be performed as quickly as possible to ensure effective treatment. Determining the etiology of sepsis is crucial for selecting the most appropriate pharmacotherapy or alternative personalized treatment methods. Current clinical practice relies on established scoring systems, specifically NEWS, MEWS, SOFA, and qSOFA. These scales have greatly improved the speed of diagnosis. Nevertheless, ongoing efforts should focus on further reducing the diagnostic timeframe, as sepsis remains a critical, life-threatening condition.
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## Definitions and historical review

Sepsis is organ dysfunction caused by dysregulated host response to infection. As a diagnostic criterion for sepsis, rapid increase in Sequential [Sepsis-related]. Organ Failure Assessment score (SOFA) by at least 2 points is recognized [1]. Septic shock is defined as a subtype of sepsis characterized by profound abnormalities in circulation, metabolism, and cell function, resulting in higher mortality risk compared to sepsis alone. It can be diagnosed in adult patients with hypotension requiring vasopressor therapy to maintain mean arterial pressure ≥65 mmHg, and serum lactate level >2 mmol/L (>18 mg/dL) despite adequate fluid resuscitation [2].

The first universal definition of sepsis and related conditions emerged during a consensus conference in the USA in 1991 and was published in 1992 [3]. It depicted sepsis as a systemic inflammatory response syndrome (SIRS) to infection. The term "severe sepsis" corresponded to sepsis with organ dysfunction, while septic shock was defined as a subtype of severe sepsis with hypotension and perfusion abnormalities or organ dysfunction despite adequate oxygen delivery. Discontinuation of the terms "septicemia" and "sepsis syndrome" was recommended. Septicemia referred to the presence of microorganisms or their toxins in the blood, yet the term was unclear and caused difficulties in clinical practice and data interpretation. Sepsis syndrome was used interchangeably with septic shock or other inflammatory states, sometimes unrelated to infection, leading to confusion, hence it was deemed unnecessary and recommended for discontinuation.

Awareness of the introduced definitions of sepsis was unfortunately low among physicians working in intensive care units. In a survey conducted in 2000

among physicians practicing in intensive care units, only 22% of intensive care specialists and 5% of physicians from other specialties were familiar with the consensus definition, and nearly 70% of respondents expressed concern about the lack of universally accepted sepsis definition [4]. Consequently, with the identification of new diagnostic criteria, it was decided to reevaluate the definition of sepsis. For this purpose, the International Sepsis Definition Conference was held in 2001 [5]. Specialists concluded that despite the flaws in current definitions, they should not be altered yet. The priority was to facilitate physicians in making accurate bedside diagnoses and initiating appropriate therapeutic actions, rather than creating a precise definition that would enable the development of simple criteria for inclusion in clinical trials. Instead, focus was placed on adding new symptoms to the SIRS diagnostic criteria, while maintaining the priority of treatment over research. It was already recognized at that time that organ dysfunction could be an early manifestation of sepsis, which was a significant prognostic factor. However, it was unclear whether the assessment of this condition could contribute to increasing the effectiveness of therapeutic procedures.

The following year, The Society of Critical Care Medicine (SCCM), the European Society of Intensive Care Medicine and the International Sepsis Forum initiated the Surviving Sepsis Campaign, resulting in the publication of the first guidelines for sepsis management two years later, in 2004 [6]. These guidelines are regularly updated every four years. In 2016, due to better understanding of sepsis pathomechanism as a dysregulated response to infection, currently used definitions were introduced [1]. It was recognized that the terms "sepsis" and "severe sepsis" were often used interchangeably, leading to a recommendation to discontinue the term "severe sepsis." Furthermore, clinical criteria for diagnosing septic shock were specified because the previous definition was too broad, resulting in a wide range of mortality statistics for patients with potential septic shock. The mortality rate varied between 7% and 64% within 2 electronic health record databases from University of Pittsburgh Medical Center and Kaiser Permanente Northern California [2]. Emphasis was also placed on early recognition of sepsis outside the intensive care unit, proposing the quick Sequential Organ Failure Score (qSOFA) for this purpose.

In 2021, the latest Surviving Sepsis Campaign guidelines were published, which no longer recommend the use of the qSOFA, instead suggesting the use of the National Early Warning Score (NEWS), or Modified Early Warning Score (MEWS) [7].

## Etiology of sepsis

Identifying the source of sepsis is one of the most important points, so that we can choose the best suited therapy for the individual. We also need to focus on epidemiology in the search for the source, since infections that are acquired in the ICU may differ from those that are the main reason for admission [8]. However, we still do not know the exact reasons why infections that should remain local spread beyond their environment and cause sepsis. There may be multifactorial causes, such as the direct effects of invading microorganisms or their toxic products, excess pro-inflammatory mediators released, and complement activation. In addition, some people may be genetically predisposed to develop sepsis [9].

In about 70% of hospitalized patients, sepsis is of bacterial origin. The most common cause of it, as many as half of the cases, are inflammations related to the lungs, such as pneumonias and abscesses. Others are intra-abdominal (colitis or cholangitis), bladder, kidney, skin (cellulitis or fasciitis) or meningitis [10]. For the most part, these inflammations are controlled by the host organism and remain a balanced response that is infection. However, when the infection spreads rapidly, and in addition, there are various predisposing factors that can lead to sepsis [11]. However, less than half of blood and urine cultures are positive for detecting sepsis. The most common bacteria isolated are Staphylococcus aureus, Klebsiella pneumoniae, Neisseria meningitidis, Pseudomonas aeruginosa or Escherichia coli. The gram-positive bacterium Staphylococcus aureus as the most common cause of sepsis is a result of the introduction of childhood vaccines against meningococcus and pneumococcus, as they could previously be considered the most common causes in children. Staphylococcus aureus infections have not changed significantly with the COVID-19 pandemic and associated restrictions, such as wearing masks and greater awareness of hygiene.

Gram-negative bacteria are a dangerous cause of sepsis because of the increasing prevalence of multidrug resistance in them. Among critically ill patients, respiratory tract or venous catheter infections have accounted for a large share of Gram-negative bacterial

infections. This is in contrast to the incidence of sepsis in elderly patients living in nursing homes, where urinary tract infections were the main source of infection. Patients who reside in the ICU have a high rate of Pseudomonas aeruginosa, which may be due to having undergone antibiotic therapy, thus increasing the risk of infection to this bacterium or other non-fermenting gram-negative microorganisms. Escherichia coli is the most common urinary tract-associated pathogen that causes sepsis, which starts outside the hospital. When considering the sources of sepsis, geographic region and exposure should be taken into account, where a good example is sepsis caused by Salmonella species in resource-limited countries in Asia or Africa [12].

In cases where the etiology of sepsis is not bacterial we are dealing with "culture-negative sepsis." Other reasons that may be correlated with the occurrence of sepsis are obesity, diabetes, kidney failure, liver failure, cancer, HIV infection and immunosuppressive drugs. A patient's threefold increased risk of sepsis is also associated with having already been hospitalized [10]. The incidence of sepsis caused by fungi has increased in recent years, but it is still a lower percentage than of bacterial origin, an example being candida albicans infection, which is the 4th most common cause of late-onset sepsis in newborns [13]. Emerging infections with Staphylococcus or Candida species have increased since the 1980s in the NICU, mainly due to infections associated with the equipment used there. Viruses that can cause sepsis are influenza A and B viruses, adenovirus, enteroviruses, rhinovirus or COVID-19 [14].

## Epidemiologic

Changing definitions of sepsis and research concentrated mainly in high-income countries make it difficult to provide a complete epidemiological picture of this infection. Additional research in low-income countries and high-risk subpopulations is required to fully confirm the epidemiology of sepsis. However, it is certain that since the establishment of the first definition of sepsis in 1991 (Sepsis-1) until the present time (Sepsis-3), the incidence of sepsis has been steadily increasing [8].

According to the World Health Organization, in 2017, sepsis occurred in 49 million people worldwide, and 11 million died as a result. In Poland, due to the lack of a national registry, there are no reliable data on the incidence of sepsis, which significantly hinders efforts aimed at its prevention and control. Epidemiological studies of sepsis include patients suffering from sepsis in ICU, but lots of septic patients aren't admitted to the ICU, which can be the reason of lowering the results. The actual number of sepsis cases in Poland could be 2-3 times higher [9]. According to data from the National Health Fund analyzed by the Supreme Audit Office (NIK), the number of adults hospitalized in Poland due to sepsis is approximately 20,000 annually.

Prior to COVID-19, sepsis was the most common cause of emergency admissions to hospitals and intensive care units [10].

Mortality risk of sepsis is on high-level all around the world, within a level of 40%. Not only in adults, but as well in pediatric units, for instance, in a prospective cross-sectional study conducted across 128 sites in 26 countries, the observed mortality in the pediatric group of patients with severe sepsis was:

- 21-32% in North America, Europe, Australia, and New Zealand,
- 40% in Asia,
- 11% in South America,
- 40% in South Africa.

Since 1960, the mortality rate of severe sepsis in pediatric patients in resource-rich areas has decreased significantly, dropping from 97 percent to approximately 4 to 10 percent in cases of severe sepsis, and from 13 to 34 percent in cases of septic shock [11].

## Diagnostics

The recognition of sepsis and septic shock may be problematic at first diagnosis. The clinical picture of sepsis is very variable, the differential diagnosis of sepsis is extremely wide, and the etiology of the symptoms may not be immediately obvious. Because of this, making a precise diagnosis and determining the onset of sepsis is a significant problem. Therefore, special attention should be paid to people at risk of sepsis infection. Increased risk factors include:

- age over 70,
- immunodeficiency,
- postoperative states,
- trauma,
- pregnancy and postpartum period.

The first signs of sepsis are non-specific. During physical examination of the patient the following may appear:

- body temperature > 38°C or < 36°C,
- disturbances of consciousness,
- low systolic blood pressure < 90 mmHg,
- cardiac rhythm disturbances,
- tachycardia > 120/min,
- respiratory rate > 25/min,
- lack or decreased diuresis to < 0.5 ml/kg/hour.

These symptoms define Systemic Inflammatory Response Syndrome (SIRS). It only gives a clinical picture of changes in the body, but its use enables the quick selection of patients who require detailed supervision and extended diagnostics [8].

To recognize sepsis early there are used some scales, such as EWS, NEWS, MEWS, SOFA and qSOFA. The first tool was EWS (Early Warning Scale). On its basis, the NEWS and MEWS scales were developed. NEWS and MEWS are composite scoring systems derived from six physiological parameters. Both scales investigate respiration rate, systolic blood pressure, pulse rate, level of consciousness or new confusion and temperature. The difference is in the last measured parameter - NEWS estimates oxygen saturation and MEWS, the diuresis. The SOFA score identifies organ failure in six systems (central nervous system, cardiovascular system, respiratory system, coagulation, liver and renal function) and assigns 0–4 points for each system. The qSOFA is a simplified version of the SOFA Score. Calculating the qSOFA score is straightforward as it comprises only three components, all easily identifiable at the bedside, each assigned a single point: respiratory rate ≥22/minute, altered mentation, systolic blood pressure ≤100 mmHg [12].

The qSOFA score was initially validated in 2016 as most beneficial for patients suspected of having sepsis outside of the intensive care unit (ICU). However, data comparing its performance with other mortality predictors, such as systemic inflammatory response syndrome criteria (SIRS) or the national early warning score (NEWS), are contradictory. In a retrospective review of several scores in emergency department patients with sepsis, NEWS emerged as the most accurate predictor [13].

Sepsis is assessed by various laboratory tests, including various biomarkers necessary for diagnosis, early recognition of severity, risk stratification and prognosis. To confirm sepsis, a series of laboratory studies are being done, such as:

- rapid blood glucose, arterial blood gas or venous blood gas and pulse oximetry, blood lactate,
- C-reactive protein, blood, urine or other cultures,
- complete blood count with differential (including platelet count),
- electrolytes, calcium,
- blood urea nitrogen and creatinine, total bilirubin and alanine aminotransferase, urinalysis,
- prothrombin time (PT), partial thromboplastin time (aPTT), international normalized ratio (INR), fibrinogen and D-dimer.

The functions of individual organs can be observed by monitoring specific parameters:

- Patients with sepsis often present tissue hypoperfusion and consequent lactic acidosis. An increase in blood lactate levels correlates with elevated risk of mortality or predispose to organ dysfunction.
- Elevated creatinine levels may indicate renal failure.
- A general urine examination detects bacteria or abnormal nutrient content, which is also used to analyze kidney function or detect urinary tract infections.
- Low calcium levels need to be corrected as they can affect myocardial function or vascular tone.
- Bilirubin and aminotransferase levels reflect current liver function.
- PT, aPTT, INR, fibrinogen and D-dimer levels allow for the diagnosis or exclusion of disseminated intravascular coagulation (DIC) and facilitate the detection of coagulation disorders frequently observed in sepsis [11].

Appropriate medical equipment is required to diagnose sepsis as quickly as possible. Some foundations help health care providers purchase valuable devices. In Poland, every year the WOŚP (Wielka Orkiestra Świątecznej Pomocy) foundation collects money for different charity purposes. The aim of the foundation is to engage in health protection activities, including saving the lives of sick people, promoting health, and preventive healthcare. In 2023, the foundation collected funds to fight sepsis. Thanks to the involvement of many people WOŚP collected PLN 243,000,000.00. The entire amount raised was allocated to equipment for over 200 microbiological laboratories applying for support. The equipment included automatic blood culture systems, a laminar chamber and other devices analyzing and detecting microorganisms causing sepsis. All of this was to speed up the diagnosis of sepsis [14].

## Treatment

### Antimicrobials

Antimicrobials are the most important and essential tool in the treatment of sepsis and septic shock. According to Anand Kumar, using appropriate antibiotics resulted in a survival rate of 52.0%, while the use of inappropriate antibiotics yielded only 10.3% [15]. Guidelines from the SSC in 2021 recommend the prompt administration of antibiotics in adults with possible septic shock or a high likelihood of sepsis within 1 hour of diagnosis. Before the administration of antibiotics it is highly recommended to perform a blood culture. It is essential to consider the patient's risk group and the types of microorganisms they are exposed to - MRSA, MDR, gram-negative, gram-positive, or fungal - and then select the appropriate antibiotic or antifungal treatment [16]. Early administration of appropriate antibiotic therapy is the cornerstone of treating serious infections in the ICU. Observational, prospective, and retrospective studies confirm the importance of using appropriate empirical antibiotic therapy. Depending on the group of antibiotics used, the dose and frequency of administration vary. For β-lactams, doses slightly exceeding the MIC are used, while for aminoglycosides, single, large doses per day or longer intervals in the case of renal dysfunction are recommended. Quinolones should also be administered in larger doses but at intervals [17]. In the case of Gram-negative organisms and MRSA, simultaneous use of two antibiotics should be considered [18].

However, in the case of sepsis without confirmed bacterial infection, alternative diagnoses should be sought, and empirical antibiotic therapy should be discontinued, especially if an alternative cause of sepsis is identified. In adults with possible sepsis without shock, limited rapid testing is recommended, and if there are persistent concerns about infection, antimicrobials should be administered within 3 hours of the initial diagnosis of sepsis. Antiviral agents should not be administered. In patients with sepsis, devices providing intravascular access, which are potential sources of sepsis, should be immediately removed, and alternative vascular access should be provided. For adults with preliminarily diagnosed sepsis, when the optimal duration of treatment is unclear, clinical assessment of procalcitonin and clinical assessment to decide when to discontinue antimicrobial therapy is suggested, not solely based on clinical assessment [16].

### Hemodynamic management

Persistent hypotension and tissue hypoperfusion after adequate fluid resuscitation are caused by the loss of sympathetic vascular tone. This leads to vasodilation, neurohormonal imbalance, cardiac arrest, and mitochondrial dysfunction in the body's cells. Vasopressor and inotropic agents restore oxygen delivery to tissues by increasing arterial pressure and cardiac output appropriately. The preferred blood pressure to be achieved in therapy is a mean arterial pressure of 65 mm Hg, 80-85 mmHg in individuals with chronic hypertension, and a lower value will be better tolerated in individuals with reduced systolic function, older patients, and those with end-stage liver disease [18]. To restore adequate blood pressure, crystalloid administration is recommended initially. When the patient has received a large volume of crystalloids, concurrent albumin administration is also recommended. The main drug to be administered to raise and restore normal blood pressure is norepinephrine, which has the highest efficacy among all vasopressors [16]. This drug, when administered experimentally to sheep in the hyperdynamic phase of septic shock, increased blood flow to the heart, intestines, and kidneys, effectively increasing urine output and improving creatinine clearance [19]. If norepinephrine fails to work, instead of increasing its dose, concurrent administration of vasopressin is suggested. However, if norepinephrine with vasopressin does not yield the desired effects, epinephrine should be administered concurrently. Terlipressin or levosimendan may also be considered in the treatment of low blood pressure in sepsis, but their use is supported by low-quality evidence [16].

### Renal replacement therapy

SA-AKI (Sepsis-associated acute kidney injury) occurs if AKI (acute kidney injury) symptoms develop within 7 days of sepsis diagnosis, while SI-AKI (sepsis-induced acute kidney injury) is one of the phenotypes of SA-AKI, where AKI is directly caused by the pathophysiological mechanism of sepsis. If AKI occurs more than a week after sepsis diagnosis, sepsis is likely not its cause. SA-AKI is divided into early (up to 48 hours from sepsis diagnosis) and late (from over 48 hours to 7 days from sepsis diagnosis) [20]. Innovative treatment approaches for SA-AKI and SI-AKI may include renal replacement therapy. Renal replacement therapy has been used for a long time in critically ill patients with sepsis, in whom progressive renal failure develops

despite appropriate treatment [21]. Available methods of renal replacement therapy include dialysis and, in certain situations, kidney transplantation after sever sepsis.

The two main methods of dialysis treatment are hemodialysis and peritoneal dialysis. Hemodialysis is particularly used in sepsis to reduce significant positive fluid balance, which in septic patients after fluid resuscitation can be as high as 12,5 l (it is a state of fluid overload resulting from fluid administration during resuscitation and subsequent therapies) and in other situations such as other fluid imbalances, especially those not responding to diuretics, treatment-resistant hyperkalemia, metabolic acidosis unresponsive to sodium bicarbonate administration, clinical symptoms of uremia, or poisoning with a substance that undergoes dialysis [22]. Renal replacement therapy can be administered intermittently or continuously. The method of therapy should be chosen based on the patient's clinical picture and overall symptoms. There is no single parameter indicating the use of one of the methods of hemodialysis renal replacement therapy. Both methods have their strengths and weaknesses in terms of complications that should be considered when choosing one of them. Numerous studies have shown that survival rates in both methods were comparable [16]. The advantages of intermittent hemodialysis include the absence of the need for patient anticoagulation and the possibility of short-term immobilization. In continuous hemodialysis, heparin anticoagulation or, in critically ill patients, increasingly citrate anticoagulation, is used. However, a significant complication that differentiates these two techniques, according to M Czuczwar, is the delayed return of kidney function. Induction of chronic kidney failure is much higher when using intermittent techniques than continuous techniques. It should also be noted that the higher the dose of hemodialysis received by the patient, the greater the loss of phosphates from their body (and hypophosphatemia can result in hemolysis, rhabdomyolysis, respiratory failure, left ventricular failure, and even higher mortality rates of patients). Therefore, especially in the use of continuous therapy, phosphate supplementation should be remembered. Loss of proteins (10-15 g per day) should also be taken into account in such patients and losses should be replenished. Therefore, when choosing renal replacement therapy in a patient with developing sepsis-related kidney failure, possible complications should be considered [22].

**Biomarkers**

Biomarkers can facilitate the diagnosis and monitoring of sepsis progression. They also allow distinguishing between bacterial, viral, and fungal infections or systemic sepsis from local infections, which subsequently enables the appropriate selection of antibiotics and monitoring of sepsis complications and organ dysfunction caused by it [23]. Procalcitonin is a frequently measured biomarker in sepsis. Its elevated level in the blood may indicate bacterial infections. It also helps in assessing the time to discontinue antibiotics administered to septic patients (which also reduces patient mortality), but according to Surviving Sepsis Campaign guidelines, assessing procalcitonin levels alone, unlike clinical assessment of the patient, is a weak recommendation for the use of procalcitonin to support the initiation of antimicrobial therapy [16]. Specific markers are used to detect fungal infections, such as D-beta-glucan, CAGTA, mannan antigen (in diagnosing candidiasis), or galactomannan and D-beta-glucan (in diagnosing aspergillosis) [24]. The role of determining specific cytokines (TNF, IL-1β, IL-6, IL-8, MCP-1) and antigens in diagnosing sepsis is currently being studied, and the current research focus, which promises promising results, is the study of determining combinations of different biomarkers indicating the occurrence of sepsis [25]. Biomarkers alone should not be used as the initiating factor for administering antibiotics in the case of sepsis. This decision should primarily be based on the clinical assessment of the patient [16].

**Ventilation**

Sepsis is the leading cause of hospitalization in intensive care units. In the case of sepsis, organ failure requiring support often occurs. Like any other organ, the lungs can be affected by sepsis. Therefore, appropriate treatment of sepsis should include ventilatory support, which minimizes lung damage [26]. In adults with ARDS caused by sepsis, low tidal volume ventilation strategies are recommended instead of high tidal volume ventilation. In adults with severe ARDS caused by sepsis, a target upper limit for plateau pressure of 30 cm H2O is recommended compared to higher plateau pressures. In adults with moderately severe ARDS caused by sepsis, ventilation in the prone position for more than 12 hours a day is recommended [16]. Most patients in studies on the prone position responded better with improved oxygenation and could achieve

better lung compliance. However, it is essential to consider the complication of pressure ulcers in patients lying prone. In adults with ARDS caused by sepsis, intermittent boluses of NMDA (Anti-N-methyl-D-aspartate) instead of continuous NMBA (neuromuscular blocking agents) infusion may be considered, but the recommendation is poorly supported by scientific evidence [27]. NMBA are used to block neuromuscular transmission, improve chest wall compliance, prevent respiratory dyssynchrony, and reduce peak airway pressures. When using NMBA, appropriate sedation and analgesia should also be provided to the patient [28]. In adults with severe ARDS, veno-venous ECMO (extracorporeal membrane oxygenation) can also be considered when conventional mechanical ventilation fails. ECMO is used in patients with severe respiratory failure to facilitate gas exchange in the case of treatment-resistant hypoxemia or hypercapnic respiratory acidosis. Although previous studies on the effectiveness of ECMO in ARDS in sepsis had low-quality evidence (due to their indirect nature), a recent systematic review showed that ECMO administration in specialized centers reduces patient mortality [29,30].

**Additional therapies**

In patients with sepsis, the use of low molecular weight heparin is recommended instead of unfractionated heparin in the prevention of venous thromboembolism. Critically ill patients with sepsis are at risk of deep vein thrombosis and pulmonary embolism, and the administration of appropriate pharmacological agents enables prevention of thromboembolic events. Mechanical prophylaxis should not be used instead of pharmacological prophylaxis in venous thromboembolic disease due to a possible lack of influence on treatment outcomes.

In septic patients it is better to keep glucose level no higher than ≥ 180 mg/dL (10 mmol/L).

There may also be a benefit to initiate early enteral nutrition (within 72 hours) associated with maintaining gut integrity and preventing gut permeability, suppressing the inflammatory response, and modulating metabolic responses, which may reduce insulin resistance. However, further studies are needed on this issue in patients with sepsis [16].

**Fluid therapy**

Fluid resuscitation remains a subject of debate. In patients suffering from sepsis, intravenous fluid therapy allows for maintaining or increasing cardiac output, arterial blood pressure, and circulating fluid volume. Fluid therapy is divided into four stages: resuscitation (administration of fluids to restore perfusion), optimization (benefits and risks of additional fluid administration are assessed, and whether perfusion has been restored is evaluated), stabilization (fluid therapy is used only when fluid responsiveness increases), and evacuation (removal of excess fluids accumulated during treatment) [31]. According to guidelines, in patients with sepsis-induced hypoperfusion or septic shock, the suggestion is to administer intravenous crystalloids at a dose of at least 30 mL/kg within the first three hours of diagnosis (average 10 ml/kg/h). In addition to traditional measurement methods such as physical examination, heart rate, and respiratory rate, we also use passive leg raising test, cardiac output, and capillary refill time, which are non-invasive measurements [32]. As demonstrated, individuals with abnormal capillary refill time had worse prognoses than those with normal CRT. There are two pathways of fluid therapy – liberal and restrictive [33].

Studies have shown that regardless of the chosen approach, the 90-day mortality rate remains at a similar level, approximately 14.0% for the group treated with restrictive fluid therapy and 14.9% for the group treated with liberal fluid therapy, therefore it is not possible to determine which approach is recommended [33]. In individuals qualifying for vasopressor therapy and in septic shock, the Surviving Sepsis Campaign (SSC) recommends a dose of norepinephrine or epinephrine ≥0.25 mcg/kg for at least 4 hours [7]. When the dose approaches 15 mcg/min (or 0.3 mcg/kg/min) in most patients, vasopressin is administered via central venous access, and hydrocortisone and fludrocortisone are added for a period of 7 days [34].

Studies indicate that individuals with elevated serum lactate levels have lower 30-day, 90-day, and one-year survival rates compared to those with lower lactate levels; therefore, therapy should focus on reducing lactate levels [7,35].

**Other treatment methods**

Polymyxin B hemoperfusion has been developed to neutralize circulating endotoxins in the blood, slowing the progression of sepsis. It involves the absorption of endotoxins by covalent and ionic molecules [36]. According to the 2021 SSC guidelines for adults, the use of this type of treatment is not recommended because

after excluding studies prior to 2010, mortality after this therapy is higher or remains at a similar level compared to standard therapy [7].

## Infections and sepsis

Bacterial infections are one of the causes of sepsis in patients. Bacterial sepsis is a condition in which the immune response is strong enough to damage tissues and organs in the body [37]. The SSC recommends the prompt administration of antibiotics, preferably within an hour of diagnosis.

According to the 2021 SSC guidelines, adults with low likelihood of infection and without septic shock are recommended to defer antibiotic therapy and continue monitoring the patient [7]. Infections caused by MRSA strains are particularly dangerous. As research shows, MRSA infections account for between 13 to 74 percent of all global Staphylococcus aureus infections [39]. Adults at high risk of MRSA should receive empirical antibiotic therapy targeting MRSA strains, while those at low risk should receive agents that do not target MRSA strains [7]. As for infections caused by gram--negative bacteria, studies suggest that double antibiotics are not necessary; however, some administer high doses of an aminoglycoside with another antibiotic to quickly kill pathogens [40].

## Summary

In our work, we focused on the treatment, especially in the first hours of sepsis, which should be based on identifying the source and cause of sepsis as soon as possible and combating it. The diagnosis is based on clinical symptoms, and the patient's condition is assessed on scales, e.g. the qSOFA scale. Biomarkers should play an important role in therapeutic management and can also be used to observe disease progression, but the most important factor is always the patient's clinical condition. Fluid therapy should be considered to maintain proper hemodynamic parameters. In the case of AKI, renal replacement therapy should be considered. It is highly recommended to maintain average blood pressure at >65 mmHg. Ventilation is crucial in sepsis with ARDS. In the case of severe ARDS, the use of ECMO may also be considered, but further research in this direction is required.

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Conflict of interest
None

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