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Current Diagnosis and Treatment Approach to Sepsis

Sepsiste Güncel Tanı ve Tedavi Yaklaşımı

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Abstract

Sepsis is a major healthcare problem worldwide. Its mortality and morbidity is still high. Early diagnosis of sepsis and appropriate management in the initial hours improve outcomes. The Surviving Sepsis Campaign published new definitions for sepsis in 2016. In Sepsis-3 definitions, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total SOFA score of at least two points consequent to the infection. However, this definition is endorsed by two international societies and there is much discussion regarding new definitions. Prospective validation of this definition on different levels is needed. The infectious source in sepsis depends on patients' underlying diseases and origin of the infection (community-acquired or healthcare-associated). In the literature, urinary tract and skin-soft tissue infection are the common sites in community-acquired sepsis, whereas respiratory system and intraabdominal infections are more common in nosocomial sepsis. Another challenge in sepsis management is the increasing incidence of sepsis due to multidrug-resistant bacteria and limited treatment options. New antibiotics may be treatment options in the future. In this review, current definitions of sepsis, physiopathology of sepsis, foci of sepsis and causative microorganisms, microbiological diagnosis and rapid diagnosis methods, biomarkers used in the diagnosis of sepsis, antimicrobial treatment and resistance, new antibiotics and non-antibiotic therapy are discussed.
Keywords: Sepsis, diagnosis, treatment, new antibiotics, multidrug resistance

Öz

Sepsis tüm dünyada önemli bir sağlık problemidir. Mortalite ve morbiditesi hala yüksektir. Sepsisin erken tanısı ve saatler içinde uygun müdahale yapılması daha iyi sonuçlara neden olabilmektedir. Sepsis Sağkalım Kampanyası (the Surviving Sepsis Campaign) 2016'da yeni sepsis tanımlarını yayınlamıştır. Sepsis-3 tanımlarında, sepsis, enfeksiyona konağın verdiği kontrolsüz yanıt sonucu gelişen hayatı tehdit eden organ disfonksiyonu olarak tanımlanmıştır. Enfeksiyona bağlı gelişen organ disfonksiyonu toplam SOFA skorunda en az 2 puanlık artış ile tanımlanmıştır. Ancak bu tanım iki dernek tarafından desteklenmiş olup yeni tanımlar üzerinde pek çok tartışma vardır. Bu tanımın değişik düzeylerde prospektif validasyonu gereklidir. Sepsiste enfeksiyon odağı hastaların alt hastalıklarına ve enfeksiyonun nerede geliştiğine (toplum veya sağlık hizmeti ilişkili) göre değişmektedir. Pek

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çok seride toplum kaynaklı sepsiste sık görülen odaklar üriner sistem ve yumuşak doku enfeksiyonu iken, nozokomiyal sepsiste sık görülen odaklar solunum sistemi ve intra-abdominal enfeksiyonlardır. Sepsis tedavisinde diğer bir problem, çok ilaca dirençli bakteriye bağlı sepsis insidansının artması ve tedavi seçeneklerinin kısıtlı olmasıdır. Gelecekte yeni antibiyotikler tedavi seçeneği olabilir. Bu derlemede sepsis tanısında güncel tanımlar, sepsis fizyopatolojisi, sepsis odakları ve etkenler, mikrobiyolojik tanı ve hızlı tanı yöntemleri, sepsis tanısında kullanılan biyobelirteçler, antimikrobiyal tedavi ve direnç, yeni antibiyotikler ve antibiyotik dışı tedaviden bahsedilmiştir.
Anahtar Kelimeler: Sepsis, tanı, tedavi, yeni antibiyotikler, çok ilaca direnç

Introduction

Sepsis is a syndrome characterized by uncontrolled host inflammatory response to an infection, which leads to organ failure[1]. Sepsis continues to be an important problem in modern medicine. The incidence of sepsis in developed countries has increased over time. Reports indicate that in the United States of America, approximately 750,000 people are affected by sepsis and about 300,000 people who present to emergency departments are diagnosed with sepsis annually[2]. The true incidence of sepsis in developing countries is unknown, but it is believed to account for 2-11% of all hospital and intensive care unit (ICU) admissions[3]. The rising incidence of sepsis has been attributed to advances in medical technology, growth of the elderly population, greater numbers of critical care patients and invasive procedures, the growing number of patients undergoing immunosuppression and transplantation, and extended life expectancy in patients with comorbidities[4-6]. Despite advances in sepsis management and early administration of targeted therapies, the mortality rate is still high. Mortality rates of 20-80% have been reported in different studies[7-9]. Mortality is higher among patients with advanced stages of sepsis, advanced age, and comorbidities[9-12]. Early diagnosis and treatment are important to reduce sepsis-related mortality. This review discusses current definitions in sepsis diagnosis, the physiopathology of sepsis, septic foci vs. etiologic agents, microbiological and rapid diagnostic methods, diagnostic biomarkers, antimicrobial treatment and resistance, new antibiotics, and non-antibiotic treatment.

Current Definitions

Various terms have been used in reference to sepsis and its clinical presentations, including bacteremia, septicemia, sepsis, sepsis syndrome, and septic shock. The lack of consensus on the definition of sepsis results in major differences when comparing incidence rates and treatment results between different studies. The American College of Chest Physicians and the Society of Critical Care Medicine (SCCM) reviewed definitions related to sepsis in their consensus conference in 1991[13]. In this meeting, a definition of infection was established for sepsis and systemic inflammatory response syndrome (SIRS) was defined. Levels of severity were defined as sepsis, severe sepsis, and septic shock. The terms septicemia, sepsis syndrome, and refractory shock were not recommended because they were considered confusing and unspecific. In this conference, the term SIRS was created to refer to disseminated inflammation. Criteria for SIRS were defined as: a) body temperature >38.3 °C or <36 °C, b) tachycardia (>90 beats/min), c) tachypnea (>20 breaths/min), and d) white blood cell count >12,000/µL or <4,000/µL, or >10% immature cells. In cases of suspected or confirmed infection, the presence of at least 2 SIRS criteria is considered sufficient for sepsis diagnosis. This clinical presentation is not a specific definition because it is seen in many hospitalized patients and may occur due to various noninfectious causes, such as pancreatitis, burns, or trauma. The signs and symptoms of SIRS are not sufficient to distinguish between infectious and noninfectious causes of SIRS. Moreover, using SIRS criteria to diagnose infection may not be reliable for newborns, patients who have recently undergone surgery, and those with trauma, burns, pancreatitis, neutropenia, or organ transplantation. In addition, not all patients with infection develop a systemic response. Therefore, the definition of sepsis used here was not considered adequate.

In the following years, sepsis definitions were reviewed and amended with certain clinical and laboratory criteria in order to enhance their specificity and sensitivity. However, the authors stated these definitions were also not gold standards and the suggestions were intended to assist clinicians when making decisions at the bedside[14]. The need to develop new sepsis criteria arose as a result of increased recognition of sepsis, the growing number of sepsis patients being treated in ICUs, and our better understanding of the pathophysiological mechanisms underlying sepsis. The SCCM updated its sepsis definitions in 2016 in the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). They defined evaluation scores for predicting the risk of sepsis-related death in patients within or outside the ICU[1]. Sepsis was defined as life-threatening organ dysfunction characterized by an increase of at least 2 points in "Sequential (Sepsis-related) Organ Failure Assessment (SOFA)" score in patients with suspected infection. Sequential (Sepsis-related) Organ Failure Assessment score includes PaO_2/FiO_2, Glasgow Coma Scale, mean arterial pressure (MAP), serum creatinine, urine output, bilirubin level, and platelet count. The definition of septic shock was revised to include fluid-resistant hypotension, serum lactate level higher than 2 mmol/L (>18 mg/dL), and the need for vasopressor therapy to maintain MAP

≥65 mmHg. The most important change in the sepsis definitions was that the nonspecific terms SIRS and severe sepsis were eliminated, because the new definitions of sepsis and septic shock encompass patients with evidence of hypoperfusion and organ dysfunction. Multiorgan dysfunction syndrome describes progressive organ failure in which homeostasis cannot be maintained without intervention. Past versions of the sepsis and septic shock definitions are shown in Table 1.

The quick SOFA (qSOFA) is a new bedside index and modified version of the SOFA score which includes 3 parameters: a) respiratory rate ≥22/min, b) systolic blood pressure ≤100 mmHg, and c) altered mental status (Glasgow Coma Scale score <13). The presence of at least 2 of these 3 criteria has been associated with sepsis-related mortality. Since the qSOFA was developed retrospectively from databases, prospective validation of its prediction of real-life sepsis-related death is needed. An analysis of the predictive validity of the SOFA score included in the new definition of sepsis, the SIRS criteria, the LODS (Logistic Organ Dysfunction System) score, and the qSOFA revealed two main findings[15]. Firstly, in ICU patients, the predictive value of SOFA score for hospital mortality was not significantly different from that of the LODS score but was superior to that of the SIRS criteria. This finding supports the use of SOFA as a clinical criterion of sepsis. Secondly, for patients outside the ICU, qSOFA score had significantly higher predictive value for hospital mortality compared to SIRS criteria. This suggests that it may be used to support a probable diagnosis of sepsis.

SOFA score is an organ dysfunction score. It is not pathognomonic for sepsis and does not discriminate organ dysfunction related to infectious or noninfectious causes. It only helps identify patients with high risk of infection-related death. Mortality rates among patients who meet the SOFA criteria for sepsis and septic shock are ≥10% and ≥40%, respectively[16].

The updated SCCM Sepsis-3 definitions are not endorsed by the Infectious Diseases Society of America (IDSA) or emergency medicine societies, mainly because the new definitions are not prospectively validated for patients outside the ICU. Criticism primarily focuses on the very low rates of proven infection in the studies on which the new sepsis definition is based. Infection could not be confirmed in approximately 40% of the patients admitted to the ICU[17]. Based on the Sepsis-3 definitions, many patients admitted to the ICU for organ failure and shock may be given broad-spectrum antibiotics, potentially leading to unnecessary antibiotic use in the ICU. On the other hand, treatment of patients with bloodstream infection and qSOFA score <2 may be delayed. Furthermore, qSOFA is not a diagnostic score for sepsis, but only a prognostic score. Therefore, using the SIRS criteria in emergency departments and general ward settings is considered more useful in sepsis screening[18].

In addition to these criticisms, the Sepsis-3 definitions were based on the data of adult patients in high-income countries. It has yet to be determined how well these new definitions will predict sepsis mortality and morbidity in low- to medium-income countries. For example, the inclusion of serum lactate level in the definition of septic shock may present a problem for countries with limited resources[19,20]. Therefore, these definitions should be evaluated for use in patients in other countries.

Although definitions of sepsis may evolve, early diagnosis and treatment may be possible through education and awareness campaigns about sepsis.

Pathophysiology

The normal host response to infection is a complex process which begins repairing damaged tissue while simultaneously controlling the bacterial invasion. This response includes the activation of phagocytic cells and synthesis of proinflammatory and antiinflammatory mediators. In sepsis, however, the host

Table 1. Definitions of sepsis and septic shock[13-15]

	Sepsis	Septic shock
1991 Sepsis-1	**SIRS:** - Body temperature >38.3 °C or <36 °C, - Tachycardia (>90 beats/min), - Tachypnea (>20/min), - White blood cell count >12,000/μL or <4,000/μL, or >10% immature cells	**Severe sepsis** Sepsis with organ dysfunction in at least one of the following systems: - Cardiovascular (hypotension/hypoperfusion) - Renal (oliguria) - Respiratory - Hepatic - Hematologic - Central nervous system (alterations in mental status) - Unexplained metabolic acidosis
1991 Sepsis-1	Suspected/confirmed infection + ≥2 SIRS criteria	Sepsis/severe sepsis + hypotension despite adequate fluid support
2001 Sepsis-2	Suspected/confirmed infection + ≥2 SIRS criteria	Sepsis/severe sepsis + hypotension despite adequate fluid support
2016 Sepsis-3	Suspected/confirmed infection + SOFA ≥2	Sepsis + fluid-refractory hypotension: - Lactate >2 mmol/L - Vasopressor for MAP ≥65 mmHg

SIRS: Systemic Inflammatory Response syndrome, SOFA: Sequential/Sepsis-related Organ Failure Assesment, MAP: Mean arterial pressure

exhibits an extreme response to the infection that can adversely affect the damaged area or normal tissues remote from the infection site[21].

The normal response to infection begins when natural immune cells, particularly macrophages, recognize and bind bacterial components. Pattern recognition receptors found on host immune cells bind pathogen-associated molecular patterns present in microorganisms[22]. Pattern recognition receptor may also recognize endogenous signals from within the cell. These danger-associated molecular patterns, known as DAMP, may be nuclear, cytoplasmic, or mitochondrial and are released during the inflammatory response[23]. The binding of microbial components by immune cells activates certain mechanisms. One of these is triggering a signaling pathway by activating cytosolic nuclear factor-kappa B (NF-kB). Activated NF-kB translocates to the nucleus and binds to transcription binding sites to activate the transcription of a large group of genes that are involved in the inflammatory response. Among these are proinflammatory cytokines [tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1)], chemokines (intracellular adhesion molecule-1, vascular cell adhesion molecule-1), and nitric acid. Polymorphonuclear leukocytes (PMNL) and endothelium are also activated to express adhesion molecules that mediate leukocyte marginalization and aggregation on the vascular endothelium, and the leukocytes migrate to the site of tissue damage. Mediators secreted by PMNL cause the main signs of local inflammation: heat, edema and hyperemia associated with local vasodilatation, and protein-rich edema due to increased microvascular permeability. These events are regulated by proinflammatory and antiinflammatory mediators secreted by macrophages[24-26].

Tumor necrosis factor-alpha and IL-1 are among the most important proinflammatory cytokines. While TNF-α release is autocrine, the non-TNF cytokines and mediators (IL-1, IL-2, IL-6, IL-8, IL-10, platelet activating factor, interferon, and eicosanoids) increase levels of other mediators. Cytokines that inhibit the release of TNF-α and IL-1 are considered antiinflammatory. The balanced action of proinflammatory and antiinflammatory cytokines regulates inflammatory response and results in tissue repair[27].

Sepsis develops when the proinflammatory cytokine response extends beyond local limits, causing a systemic response. Sepsis can be regarded as increased intravascular inflammation. It is still unclear why the inflammatory response usually remains local but occasionally spreads to cause sepsis. Multiple factors seem to be involved, including the microorganisms' direct effect (endotoxin, peptidoglycan, lipoteicoic acid) or toxins, excessive release of proinflammatory mediators, complement activation, and genetic predisposition of the host. Tumor necrosis factor-alpha and IL-1 cause fever, hypotension, leukocytosis, activation of coagulation, and fibrinolysis. There is also evidence that complement system activation plays an important role in sepsis[28-32]. Single-nucleotide polymorphism is the most common genetic variation. Single-nucleotide polymorphisms that increase susceptibility to infection and are associated with poor prognosis are located in the genes encoding cytokines, cell surface receptors, lipopolysaccharide ligands, mannose-binding lectin, and heat shock protein-70[33].

The systemic effects of sepsis include tissue ischemia, cytopathic damage, altered apoptosis rates, mitochondrial dysfunction, and immunosuppression. Microcirculation is disrupted, proinflammatory mediators and inflammation products cause mitochondrial dysfunction and lead to cytotoxicity. This eventually results in organ dysfunction. The presence of proinflammatory cytokines during sepsis may delay the apoptosis of macrophages and leucocytes, and contribute to prolonged inflammatory response. Sepsis is a cytokine storm which is followed by immunosuppression due to the inability to release proinflammatory cytokines and the increased expression of inhibitory receptors and ligands[34-36].

Sepsis affects various organ systems. In the cardiovascular system, the release of vasoactive mediators (prostacyclin, nitric oxide) causes vasodilation while disrupted release of vasopressin, and redistribution of intravascular fluid, results in hypotension. The release of myocardial depressants reduces systolic and diastolic ventricular performance. Endothelial damage, coagulation disorders, and endothelial dysfunction associated with bacteria cell wall and components also contribute to tissue edema[34,35,37]. In the respiratory system, endothelial damage in the pulmonary vasculature disrupts blood flow, increases microvascular permeability, and leads to interstitial and alveolar pulmonary edema. Leukocyte trapping in the microcirculation initiates and perpetuates alveolocapillary membrane damage. Pulmonary edema, ventilation-perfusion mismatch, hypoxemia, and acute respiratory distress syndrome develop. Intestinal barrier dysfunction allows the translocation of bacteria and endotoxins into the systemic circulation, prolonging the septic response. The liver is the first line of defense against bacteria and toxins; liver dysfunction prevents their elimination and enables them to enter the circulation. Sepsis is often accompanied by acute kidney failure due to acute tubular necrosis secondary to hypoperfusion or hypoxemia. Systemic hypotension, renal vasoconstriction, cytokine release, neutrophil activation, and chemotactic peptide may also be involved. Central nervous system complications are also common. Encephalopathy is the most frequent complication and is associated with changes in metabolism and cellular transmission. Blood-brain barrier disruption and mitochondrial dysfunction occur. The parasympathetic nerveous system is also believed to be a mediator of inflammation during sepsis[34,35,38-40].

In summary, sepsis occurs when the response to infection extends beyond local boundaries, and is characterized by excessive production of proinflammatory cytokines. Cellular damage is the precursor mechanism to organ dysfunction.

Sites of Infection and Etiologic Agents of Sepsis

The prevalence of different infectious foci in sepsis studies varies with the patient group and the definitions used. Approximately 53-66% of sepsis cases are community-acquired, though an increase in cases of hospital-acquired sepsis has been reported in recent years[41,42]. Studies of community-acquired sepsis have determined the urinary tract to be the most common focal site, whereas the lower respiratory system and intraabdominal infections were reportedly the most common foci in studies including patients in intensive care and with hospital-acquired sepsis. In the community-acquired sepsis and septic shock cases published by Storgaard et al.[43], urinary tract infection (UTI) was the most common focal site, with 36%. In a study conducted in Turkey, Güler et al.[44] also reported that UTI was the most common infection site in community-acquired sepsis (45%), followed by respiratory system infection (13%), intraabdominal infection (9.6%), and skin and soft tissue infection (5%). However, according to the Extended Prevalence of Infection in Intensive Care II (EPIC II) study, respiratory system infections accounted for about 64% of all infections in ICU patients with sepsis, followed by intraabdominal (20%), bloodstream (15%), and genitourinary system infections (14%)[45]. Similarly, respiratory tract infections were also responsible for most cases of severe sepsis in the EPISEPSIS study[46]. Therefore, the lungs, abdomen, and urinary tract should be evaluated first as potential infectious focal sites in patients with suspected sepsis. Other rarely reported septic foci are intravascular catheter (1.4%-10.5%), surgical site infection (1.1%-6%), neurosepsis (0.4-3%), and cardiac sepsis (0.4%-0.6%)[47-52]. Moreover, multiple foci have been identified as sources of sepsis in 12.5-33.1% of patients[52,53], and no infectious focus could be detected in 8-22% of patients (Tables 2, 3)[43,49,52].

The causative agents of sepsis vary depending on the infection site, source of infection (community-acquired, hospital-acquired, ICU-acquired), patient characteristics (e.g. immunosuppressive, history of antibiotic use, presence of catheter), and year. Table 4 shows the causative microorganisms according to the septic foci and source of infection. Gram-positive bacteria are often the causative agents in community-acquired sepsis (56.2%), whereas Gram-negative bacteria are the primary agents in hospital-acquired sepsis (80%)[54]. In the EPIC II study conducted in ICUs, 70% of the infected patients had positive cultures, and Gram-negative microorganisms were more common than Gram-positive microorganisms (62% versus 47%). However, it was shown that *Staphylococcus aureus* was responsible for 20.5% and *Pseudomonas* spp. species for 20% of the infections[45]. Another sepsis epidemiology study by Martin et al.[55] revealed that the primary microorganisms causing sepsis between 1979 and 1987 were Gram-negative bacteria, while in the 2000s Gram-positive bacteria were detected in 52.1% of patients, Gram-negative bacteria in 37.6%, fungi in 4.6%, and anaerobic bacteria in 1%. The rate of polymicrobial infection in that study was 4.7%. The prevalence of multidrug resistant (MDR) microorganisms was 9.4% in community-acquired infections, but increased to 20.7% in hospital-acquired sepsis and to 59.1% in ICU-acquired sepsis[42].

Infectious focus is one of the important parameters determining the prognosis of sepsis. Cases in which the septic focus is the lungs or abdomen, there are multiple foci, or the focus is unknown have higher mortality rates than those caused by UTI[47,50,53]. A study by Jeganathan et al.[52] analyzing the association between mortality and source of infection showed that mortality was higher in sepsis due to pulmonary sources

Table 2. Most common infectious foci in sepsis identified in various studies (%)[44-52]

	Respiratory system	Intra-abdominal	Urinary tract	Bloodstream	Skin and soft tissue/bone
Angus et al.[51]	44	9	9	17	7
Tanriover et al.[54]	45	28	13		26
Karlsson et al.[49]	43	32	5		10
Blanco et al.[42]	45	32	6		3
Beale et al.[50]	43	23	8	6	6
Vincent et al.[45]	64	20	14	15	
Güler et al.[44]	18	10	45		5
Shen et al.[48]	49	7	28		4
Tolsma et al.[53]	19	15	6		
Leligdowicz et al.[47]	40	31	11	5	8
Kübler et al.[41]	28	49	6	8	
Jeganathan et al.[52]	21	19	18		7

[odds ratio (OR): 5.56], intravascular catheter as the source (OR: 9.15), unknown source (OR: 10.44), and multiple sources (OR: 13.35) compared to genitourinary sources. The impact of the causative microorganism on mortality is unclear. There are studies reporting that mortality is higher in Gram-negative bacteremia compared to Gram-positive bacteremia[56,57]. Among the most common causative microorganisms, *S. aureus* and *Pseudomonas* spp. are associated with higher mortality while *E. coli* and enterococci have lower mortality[58]. In multivariate logistic regression analysis of the EPIC II study, *Enterococcus* spp. (OR: 1.56), *Pseudomonas* spp. (OR: 1.38), and *Acinetobacter* spp. (OR: 1.53) infections were identified as independent risk factors for hospital mortality[45]. Mortality is also high with anaerobic and fungal pathogens and in multidrug-resistant (MDR) bacterial infections. The mortality rate is 34.5% for anaerobes, 31.4% for fungal pathogens, 12.8% in hospital-acquired sepsis caused by MDR microorganisms, while it rises to 32.7% in ICU-acquired sepsis[58,59].

Microbiological and Rapid Diagnostic Methods for Sepsis

Rapid diagnosis of sepsis is currently among the top priorities of microbiology laboratories[60]. The laboratory contributes significantly to sepsis diagnosis. Biochemistry laboratories can return results in the same day, whereas microbiology laboratory results may not be available for hours, days, or even weeks depending on the type of microorganism. Blood cultures are currently considered to be the gold standard but have some limitations in terms of their contribution to diagnosis. Firstly, following 12-18 hours of incubation, another 48-72 hours is required for identification and antibiogram of the cultures. Besides, it may be impossible or difficult to detect bacteria that are not easily cultured such as *Bartonella*, *Borrelia*, *Brucella*, *Campylobacter*, *Helicobacter*, *Coxiella*, *Legionella*, *Leptospira*, *Mycobacterium*, *Mycoplasma*, *Nocardia*, and *Rickettsia* strains. Furthermore, growth may be inhibited due to antibiotics used by the patient, and results may differ depending on blood sample volume and number of sets, microorganism load in the sample, handling of the sample, and the experience of the person interpreting the results[61].

Rapid molecular diagnostic tests are being developed and used in microbiology laboratories to facilitate accurate, rapid diagnosis and selection of correct antimicrobial treatment, prevent unnecessary antibiotic use, reduce antimicrobial resistance, and lower mortality and costs[62]. These rapid molecular diagnostic tests can be broadly categorized into two groups, culture-dependent and culture-independent.

Table 3. Common causative agents of sepsis identified in various studies (%)[44-52]

	Gram-negative bacteria	Gram-positive bacteria	Anaerobic bacteria	Fungi	Parasites	Viruses
Tanriover et al.[54]	66	34				
Karlsson et al.[49]	33	59		4		
Blanco et al.[42]	50	40		6		
Vincent et al.[45]	62	47	5	4	1	
Beale et al.[50]	41	34		9	<1	1
Leligdowicz et al.[47]	34	26	3			
Kübler et al.[41]	58	34		16		1

Table 4. Major causative pathogens according to septic focus

Septic focus	Major community-acquired pathogens	Main hospital-acquired pathogens
Lungs	*Streptococcus pneumoniae* *Haemophilus influenzae* *Legionella* spp. *Chlamydia pneumoniae*	Aerobic Gram-negative bacilli
Intraabdominal	*Escherichia coli* *Bacteroides fragilis*	Aerobic Gram-negative bacilli Anaerobes *Candida* spp.
Skin/soft tissue	*Streptococcus pyogenes* *Staphylococcus aureus* Polymicrobial	*Staphylococcus aureus* Aerobic Gram-negative bacilli
Urinary tract	*Escherichia coli* *Klebsiella* spp. *Enterobacter* spp. *Proteus* spp. VRE	Aerobic Gram-negative bacilli Enterococci

VRE: Vancomycin-resistant enterococcus

Performing culture-dependent tests first requires the detection of growth in blood cultures. This requires a minimum incubation period of 8-12 hours, which is a disadvantage. Culture-dependent diagnostic tests are summarized in Table 5. Culture-independent tests are done directly on the blood and most involve polymerase chain reaction (PCR)-based methods. The main advantages of PCR-based methods are high sensitivity and the capacity to detect as little as 1 colony-forming unit/ml of microorganism from a very small volume of blood. However, disadvantages are that the results are affected by PCR inhibitors in the sample, nonmicroorganismal nucleic acid load, contaminant DNA, and the amount of DNA in dead microorganisms. In addition, performing the tests requires experienced personnel and specialized equipment[63]. Culture-independent diagnostic methods are summarized in Table 6.

The initial expenses associated with rapid molecular diagnostic tests (device and kits costs) are quite high. However, their potential to reduce medical costs should also be considered when estimating the financial burden of these tests on healthcare institutions. The use of these tests was found to reduce antimicrobial usage, length of stay in hospital and ICU, and mortality rate[64,65].

Since sepsis diagnosis and treatment is a collaborative effort, clinicians should maintain continuous, real-time dialogue with the microbiology laboratory. Selection of the appropriate rapid diagnostic test should be based on the availability in the healthcare institution. Rapid diagnostic methods are not sufficient alone to diagnose sepsis; however, this testing should be incorporated into antimicrobial management programs implemented in hospitals.

Biomarkers in the Diagnosis of Sepsis

The clinical and laboratory findings of sepsis (e.g. fever or leukocytosis) are generally not specific. More typical signs or laboratory parameters (e.g. arterial hypotension or lactate) are often late symptoms and indicate progression towards organ dysfunction and mortality. Therefore, better sepsis markers are needed for use in clinical practice[66].

A biomarker is "a biological characteristic, objectively measured (i.e., with acceptable accuracy and reproducibility) and used as an indicator for a physiological or pathological process, or of the activity of a medicine." Biomarkers are generally classified in two categories, prognostic and predictive. Prognostic markers allow the classification of patients' chance/risk of reaching a certain outcome independent of treatment. Predictive markers allow the prediction of potential benefit (efficacy) and/or risks (toxicity) of a therapy depending on biomarker status[67].

Two of these biomarkers, C-reactive protein (CRP) and procalcitonin (PCT), meet most of the criteria expected of a good biomarker and are routinely used in many laboratories. C-reactive protein is an acute phase protein synthesized in the liver in the presence of tissue damage and inflammation. C-reactive protein synthesis is mediated by cytokines such as TNF-α, IL-6, and IL-1β. It binds to pathogen polysaccharides to activate the classical complement pathway. Procalcitonin, the prehormone of calcitonin, is normally produced by thyroid

Table 6. Culture-independent tests performed directly on blood

The LightCycler SeptiFAST test (Roche Diagnostics, Mannheim, Germany)
The SepsiTest (Molzym GmbH, Bremen, Germany)
The VYOO assay (Analytik Jena, Jena, Germany)
The Magicplex Sepsis Real-time system (Seegene Seoul, Korea)
T2 Magnetic Resonance Assay (T2 Biosystems, Lexington, MA)
IRIDICA BAC-BSI Assay (Abbott Molecular, Carlsbad, CA)
LiDia (DNAe Electronics, Carlsbad, CA)
MinION nanopore sequencing (Oxford NanoporeTechnologies, Oxford, UK)

Table 5. Culture-dependent methods (using positive blood culture flasks)

Non-amplified methods		**Amplified methods**	
Pathogen-specific methods	Fluid-based methods	Pathogen-specific real-time methods	Liquid-based technologies
Peptide nucleic acid **PNA-(FISH) technology** (AdvanDx, Woburn, MA)	**Verigene Blood Culture** Nucleic Acid Test (Nanosphere, Northbrook, IL)	**BD GeneOhm StaphSR** assay (BD Diagnostics, Sparks, MD)	**Prove-It Sepsis**
			StripAssay (Mobidiag, Helsinki, Finland)
AccuProbe System (Gen-Probe, USA)		**Xpert MRSA/SA blood**	**FilmArray Blood Culture** Identification (bioMérieux Marcy l'Etoile, France)
		Culture assay (Cepheid, Sunnyvale, CA)	
Accelerate Pheno Sytem (Accelarete Diagnostic, Arizona, USA)		**Eazyplex® test system** (Amplex ByoSistems, GmbH)	
MALDI-TOF systems			
MALDI Biotyper (Bruker Daltonics, Bremen, Germany), Saramis (AnagnosTec, Potsdam, Germany)			
The Andromas (Andromas, Paris, France), and Vitek **MS** (bioMérieux, Marcy l'Etoile, France)			

C cells in response to hypercalcemia at negligible levels. It is believed that PCT is also produced by the liver and peripheral blood mononuclear cells, regulated by lipopolysaccharides and sepsis-related cytokines. In numerous studies, PCT was found to have higher overall accuracy than CRP in differentiating bacterial infections from viral infections and between bacterial infections and other causes of systemic inflammation. Procalcitonin level was determined to be more sensitive (88% vs. 75%) and more specific (81% vs. 67%) than CRP in differentiating bacterial infection from noninfectious inflammation[68]. Its high sensitivity and specificity, short half-life (<24 hours), and easy measurability make PCT a good biomarker.

Cytokines are important mediators in the pathophysiology of sepsis and are commonly evaluated as potential sepsis biomarkers because most are produced immediately upon onset of sepsis. Proinflammatory cytokines IL-1β and IL-6 and the proinflammatory chemokine IL-8 play an important role in initiating the natural immune response to infection and tissue damage. However, studies have shown that although these proinflammatory biomarkers are elevated in patients with severe sepsis and septic shock, they are not diagnostically superior to PCT[69,70]. The antiinflammatory cytokine IL-10 is produced by T helper cells and inhibits IL-1, IL-6, and TNF-α release. Elevated IL-10 levels indicate acute phase reaction in parallel to CRP levels.

Triggering receptor expressed on myeloid cells-1 (TREM-1), a member of the immunoglobulin superfamily, is overexpressed by phagocytic cells in the presence of bacteria or fungi, but no increase is seen in noninfectious inflammation. It stands out as a biomarker with strong prognostic value due to its ability to distinguish sepsis from SIRS[71].

Other molecules studied as biomarkers include adrenomedullin, provasopressin, natriuretic peptides (ANP and BNP), endotelin-1, neopterin, proadrenomedullin, and presepsin (CD-14). Various studies investigating presepsin as a biomarker have demonstrated that it has high sensitivity (80.1%) and specificity (81.0%) and may be helpful in distinguishing between SIRS and sepsis due to bacterial infection[67,72].

MicroRNAs (miRNAs) are small, non-protein-coding RNAs that regulate gene expression by inhibiting the translation or transcription of target mRNAs. Recent studies indicate that the spectrum of circulating miRNAs may change during various pathological conditions such as inflammation, infection, and sepsis[73]. Before they can be used in routine practice, further research is needed to clarify the biochemical and immunological processes associated with these molecules in humans.

Antimicrobial Therapy

Antimicrobial therapy forms the basis of sepsis treatment. In all patients with suspected sepsis, appropriate empirical antimicrobial therapy should be initiated as early as possible after obtaining samples for blood cultures and cultures from other possible sources. Delays in antimicrobial therapy are associated with higher mortality in sepsis[74,75]. Kumar et al.[60] showed that each hour of delay in antimicrobial therapy was associated with a 7.6% decrease in survival in patients with septic shock.

Appropriate initial empirical antimicrobial therapy increases the success of sepsis treatment[76-78]. Selection of a suitable antimicrobial agent should be based on the clinical condition of the patient, the suspected or existing focus of infection, whether the infection is community-acquired or hospital-acquired, the patient's age, and comorbid diseases (e.g. chronic obstructive pulmonary disease, chronic renal failure, chronic liver disease, diabetes mellitus, immunosuppressive conditions). Other important considerations in terms of resistant bacterial infections are the patient's history of antibiotic use in the last three months, known history of microbial colonization, immunodeficiency status, and local epidemiological data[79]. Sepsis stage rather than resistance of the infectious agent was found to be a better predictor of mortality In sepsis patients started on appropriate empirical therapy[80].

Initial empirical therapy should consist of one or more broad-spectrum agents with coverage against possible microorganisms. Antimicrobial agents recommended for initial empirical therapy based on infectious focus are presented in Table 7. In a meta-analysis, beta-lactam and aminoglycoside combination therapy was not shown to be superior to beta-lactam monotherapy for sepsis, and monotherapy was associated with decreased nephrotoxicity[81].

In another study, meropenem + moxifloxacin combination therapy was not superior to monotherapy in sepsis and septic shock unless antimicrobial resistance was involved[82]. However, there are also studies showing that early combination therapy is associated with lower mortality in patients with septic shock[83]. Combination therapy is preferred when treating sepsis patients for whom carbapenem-resistant *Enterobacteriaceae* (CRE) is considered the causative agent, due to its synergistic effect and to prevent the development of resistance[84]. Combination therapy with aminoglycoside has been associated with higher survival rates in cases of sepsis and septic shock due to Gram-negative bacteria with high risk of MDR, such as *Pseudomonas* spp. and *Acinetobacter* spp.[85,86]. Appropriate empirical therapy and combination therapy for carbapenemase-producing *K. pneumoniae* infections has also been associated with reduced mortality[87].

Table 7. Antimicrobial agents recommended for empirical therapy in sepsis based on infectious focus and risk factors for multidrug-resistant infections, *Listeria monocytogenes* in meningitis and fungemia[78,80,81,83,86,89,90,145]

Presumed infectious focus	Absence of risk factors for resistant bacterial infections	Presence of risk factors for resistant bacterial infections
Pneumonia	Ceftriaxone 2 g + clarithromycin 500 mg Levofloxacin 750 mg	Piperacillin/tazobactam 4.5 g 3 times daily ± amikacin 15 mg/kg Cefepime 2 g 3 times daily ± amikacin 15 mg/kg Meropenem 1 g 3 times daily ± amikacin 15 mg/kg **If at risk for MRSA,** Linezolid 600 mg 2 times daily can be added
Urinary tract infection	Ceftriaxone 2 g ± amikacin 15 mg/kg Ciprofloxacin 400 mg 2 times daily	Ertapenem 1 g Piperacillin/tazobactam 4.5 g 3 times daily Meropenem 1 g 3 times daily
Skin/soft tissue infection (e.g. cellulitis, erysipelas)	Cefazolin 2 g 3 times daily Ampicillin/sulbactam 3 g 4 times daily	Daptomycin 6 mg/kg Vancomycin 25-30 mg/kg loading dose followed by 15-20 mg/kg 2 times daily
Skin/soft tissue infection Gas gangrene *(Clostridium perfringens)*	**Emergency surgical debridement** Penicillin 4 MU 6 times daily + clindamycin 900 mg 3 times daily	
Skin/soft tissue infection Polymicrobial necrotizing infection (necrotizing fasciitis, pressure wound, diabetic wound, etc.)	**Emergency surgical debridement** Ciprofloxacin 400 mg 2 times daily + clindamycin 900 mg 3 times daily Piperacillin/tazobactam 4.5 g 3 times daily Meropenem 1 g 3 times daily **If at risk for MRSA** Daptomycin 6 mg/kg Vancomycin 25-30 mg/kg loading dose followed by 15-20 mg/kg 2 times daily Linezolid 600 mg 2 times daily can be added	
Intraabdominal infection	Ceftriaxone 2 g Ciprofloxacin 400 mg 2 times daily Cefepime 2 g 3 times daily + Metronidazole 15 mg/kg loading dose followed 6 hr later by 7.5 mg/kg 4 times daily OR Piperacillin/tazobactam 4.5 g 3 times daily Meropenem 1 g 3 times daily	Piperacillin/tazobactam 4.5 g 3 times daily ± amikacin 15 mg/kg Meropenem 1 g 3 times daily ± amikacin 15 mg/kg
Bacterial meningitis	Ceftriaxone 2 g 2 times daily or cefotaxime 2 g 3 times daily If penicillin susceptibility is low in *S. pneumoniae* + Vancomycin 10-20 mg/kg 2 times daily or rifampicin 600 mg once daily If there are risk factors for *Listeria monocytogenes* + Ampicillin 2 g 6 times daily	Cefepime 2 g 3 times daily Meropenem 2 g 3 times daily ± Vancomycin 25-30 mg/kg loading dose followed by 10-20 mg/kg 2 times daily
Unknown focus	Ceftriaxone 2 g Levofloxacin 750 mg	Piperacillin/tazobactam 4.5 g 3 times daily + amikacin 15 mg/kg Cefepime 2 g 3 times daily + amikacin 15 mg/kg + **If at risk for MRSA** Daptomycin 6 mg/kg Linezolid 600 mg 2 times daily Vancomycin 25-30 mg/kg loading dose followed by 15-20 mg/kg 2 times daily
If there are risk factors for fungemia	Caspofungin, 70 mg loading dose followed by 50 mg Micafungin 100 mg Anidulafungin 200 mg loading dose followed by 100 mg	
Risk factors for multidrug-resistant bacterial infections	**Risk factors for *Listeria monocytogenes***	**Risk factors for fungemia**
Hospital stay >5 days	Age >50 years	Broad-spectrum antibiotic use
Broad-spectrum antibiotic use (within last 90 days)	Diabetes mellitus	Central venous catheter
High resistance rates in the region	Use of immunosuppressive drug	**+ One of the following:**
Residency in a nursing home	Cancer	Parenteral nutrition

Table 7. Continued

Chronic dialysis (within last 30 days)	Immunosuppression due to other causes	Neutropenia
Wound care at home	Chemotherapy	Hematologic malignancy
Family member with resistant bacterial infection	Renal replacement therapy in an intensive care unit	Immunosuppression
Mechanical ventilation ≥5 days	Recent abdominal surgery	
Immunosuppression		**Candida score used according to risk factors:** Sepsis 2 points Multifocal candidiasis colonization 1 point Surgery 1 point TPN 1 point Empirical treatment for candidiasis can be initiated for scores of 3 or higher
Structural lung disease		
IV drug addiction		
COPD (*Pseudomonas* spp.)		
Superinfection (MRSA) after influenza infection		

COPD: Chronic obstructive pulmonary disease, IV: Intravenous, MRSA: Methicillin-resistant S. aureus, TPN: Total parenteral nutrition

Considering the current increases in resistance rates, carbapenems and beta-lactam + beta-lactamase inhibitors stand out as agents that can be utilized as monotherapies[88]. Combinations with vancomycin, linezolid, or for nonpulmonary foci of infection, daptomycin should be considered for cases of septic shock with methicillin-resistant staphylococci predicted as the causative agent[89]. Appropriate antibiotic combinations should be used to treat presumed infection with hospital-acquired MDR bacteria. Antifungal agents should be included in empirical therapy for patients with risk factors for candidemia. Echinocandin (caspofungin, anidulafungin, micafungin) or fluconazole is recommended for empirical antifungal therapy. Echinocandins should be preferred for sepsis and septic shock and patients with previous fluconazole use. If the isolated *Candida* species is susceptible to fluconazole and the patient's clinical symptoms are improving, switching echinocandin to fluconazole is recommended. Amphotericin B can be used if the patient is contraindicated for the use of other antifungal agents[90].

Empirically initiated broad-spectrum therapy should be narrowed according to the causative pathogen isolated in culture and its antibiotic susceptibility results. Rates of growth in blood culture are generally low in these patients (30-53%)[91,92]. Patients with no growth in culture should be assessed according to their clinical condition and antibiotic de-escalation should be implemented for eligible patients with clinical improvement. If there is no clinical improvement, the antimicrobial therapy should be reevaluated and, if necessary, the spectrum of the antimicrobial therapy should be broadened. Furthermore, source control and the appropriateness of other supportive treatment modalities should be evaluated.

Antibiotics should be administered intravenously, doses should be determined by considering their pharmacokinetic and pharmacodynamic properties, and antibiotics with good penetration into the suspected or confirmed focal site of infection should be preferred. Increased volume of distribution in these patients due to intensive fluid therapy may necessitate the administration of vancomycin and beta-lactam antibiotics at high doses and with a loading dose[92,93]. Similarly, administration of a single daily dose of aminoglycosides was found to be effective in reaching target plasma concentrations in patients without renal failure[87]. When intermittent bolus administration of beta-lactam antibiotics were compared, continuous infusion resulted in higher plasma antibiotic concentrations and clinical improvement rates (56-70% versus 34-43%)[94,95].

The recommended duration of antimicrobial therapy is 7-10 days, but longer treatment periods may be needed in patients with a delayed clinical response, an infection focus that cannot be drained, or a fungal infection[79]. There is evidence that using PCT monitoring to inform the discontinuation of antibiotic therapy for sepsis may prevent unnecessary prolonged antibiotic use, which may reduce bacterial resistance development as well as medical costs[96,97].

Antimicrobial Resistance

Antimicrobial resistance has become a major problem in the treatment of both community- and hospital-acquired infections. Resistance to antibiotics may be due to intrinsic properties (natural resistance) or changes in its genetic makeup (acquired resistance)[98].

Producing beta-lactamases against beta-lactam antibiotics is one of the principal mechanisms of resistance in many bacterial species, particularly *Enterobacteriaceae*. Extended-spectrum beta-lactamases (ESBL) are especially common in *K. pneumoniae* and *E. coli*, and are responsible for the development of resistance to broad-spectrum cephalosporins and aztreonam[98]. The rapid spread of ESBL production among pathogenic bacteria and the presence of MDR in these strains

pose serious challenges in terms of treatment. Treatment options for infections due to these strains are usually limited to carbapenems and the beta-lactam/beta-lactamase inhibitors to which they are susceptible. According to the 2016 National Hospital Infections Surveillance Network (NHISN) report published by the Turkish Public Health Institution, 48.67% of *E. coli* strains and 49.19% of *K. pneumoniae* strains across Turkey are ESBL-producing[99].

In recent years, carbapenem-hydrolyzing beta-lactamases (most commonly OXA-48 type beta-lactamase) have emerged in *Enterobacteriaceae* and *Acinetobacter* spp. species in Turkey[100]. In a 2013 study of carbapenem-resistant *K. pneumoniae* isolates in Turkey, OXA-48, NDM-1, OXA- 48, and imipenemase (IMP) were detected at rates of 91.5%, 4.3%, 1%, and 3.2%, respectively[101]. In another, multicenter study, at least one carbapenemase gene was detected by genotypic assay in 143 (92.3%) of 155 carbapenem-resistant *K. pneumoniae* and *E. coli* isolates. Single enzymes were found in 136 isolates (OXA-48: 84.6%, NDM: 6.3%, VIM: 2.8%, and IMP: 1.4%), while 7 isolates had 2 enzymes (OXA-48+NDM: 2.1%, OXA-48+VIM: 2.1%, VIM+NDM: 0.7%). The *Klebsiella pneumoniae* carbapenemase (KPC) enzyme was not detected in any of the isolates[92]. In another study published in 2016, KPC-2 carbapenemase was detected for the first time in *E. coli* isolates[102].

In addition to *K. pneumoniae* and *E. coli, Pseudomonas* spp. and *Acinetobacter* spp. species are developing resistance to most of the antibiotics used for treatment, including carbapenem and colistin, and panresistant strains have started to appear[103]. In 2016, carbapenem resistance was detected at a rate of 72.38% in *Acinetobacter baumannii* strains and 35.65% in *Pseudomonas aeruginosa* strains, while colistin resistance was detected at a rate of 3.02% in *A. baumannii* strains across Turkey[99].

Quinolone resistance has been added to the ampicillin and cotrimoxazole resistance that is high among community- and hospital-acquired UTIs, and an increase in ESBL production has been observed[104]. Some bacteria such as *P. aeruginosa* and *Proteus* spp. are inherently resistant to tigecycline due to their efflux pumps[98].

Antibiotic resistance in *S. aureus* has become increasingly important both in hospital-acquired and community-acquired infections. The rate of methicillin-resistant *S. aureus* (MRSA) was 30.9% in the SENTRY study published in 2001[105], while the MRSA rate across Turkey was detected as 38.83% in the 2016 NHISN report[99]. Vancomycin-intermediate (VISA), vancomycin-resistant (VRSA), and heterogeneous vancomycin-intermediate (hVISA) strains of *S. aureus* create serious problems in treatment[98].

Enterococci, which are part of the normal intestinal flora and are among the low virulence pathogens, have become one of the major etiological agents in hospital-acquired infections due to their natural resistance to certain antibiotics (beta-lactam and aminoglycoside resistance) and their capacity for acquired resistance (glycopeptide resistance)[106]. The 2016 NHISN report stated the prevalence of vancomycin-resistant enterococcus in Turkey as 13.33%[99].

Fluconazole resistance originating in non-albicans *Candida* strains should also be kept in mind when initiating antifungal treatment for sepsis[107].

Antimicrobial resistance greatly complicates the treatment of sepsis, leading to failure and increasing treatment costs. Therefore, the probable causative agent and its regional or hospital-specific resistance rates should be considered when selecting antibiotics to initiate therapy.

The Role of New Antibiotics in Sepsis Treatment

Infections due to MDR Gram-negative bacteria, especially in the *Enterobacteriaceae* family have risen in recent years. Treating these infections with currently available antibiotics is challenging[108]. Two new antibiotics containing novel beta-lactam/beta-lactamase inhibitor combinations ceftazidime/avibactam and ceftolozane/tazobactam are expected to be effective in treatment, and their approval in Turkey is anticipated in the near future[108].

Ceftolozane, a newly developed third generation cephalosporin antibiotic, has been combined with the beta-lactamase inhibitor tazobactam. This provides a broad spectrum of activity against many aerobic and facultative anaerobic Gram-negative bacteria, including *Enterobacteriaceae* and *P. aeruginosa*. It has been approved for the treatment of complicated intra-abdominal infection (in combination with metronidazole) and complicated UTI, including pyelonephritis[109].

With the spectrum of activity of ceftazidime combined with the beta-lactamase inhibitor avibactam, ceftazidime/avibactam exerts a bactericidal effect against many resistant Gram-negative bacteria that produce beta-lactamases, including carbapenemase[110]. This antibiotic has also been approved for the treatment of complicated intra-abdominal infection (in combination with metronidazole) and complicated UTI, including pyelonephritis. In addition, it is also approved in Europe for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia[111]. A microbiological comparison of these two antibiotics is shown in Table 8.

Both of these new antibiotics are administered intravenously and are eliminated primarily by renal excretion. Dose adjustment

Table 8. Microbiological activities of ceftolozane/tazobactam and ceftazidime/avibactam[96-98]

	Ceftolozane/tazobactam	Ceftazidime/avibactam
FDA-approved indications for use	Complicated IAI (+metronidazole) Complicated UTI (including pyelonephritis)	Complicated IAI (+metronidazole) Complicated UTI (including pyelonephritis)
Gram-negative activity	*Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa* *Enterobacter cloacae*	*Escherichia coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa* *Enterobacter cloacae* *Enterobacter aerogenes* *Citrobacter koseri* *Citrobacter freundii*
Gram-positive activity	*Streptococcus anginosus* *Streptococcus constellatus* *Streptococcus salivarius*	No activity
Anaerobic activity	*Bacteroides fragilis*	No activity
Beta-lactamase group		
Class A (TEM, SHV, CTX-M, KPC, GES)	Variable	Active including carbapenemases
Class B (NDM, VIM, IMP)	No activity	No activity
Class C (AmpC)	Variable	Active
Class D (OXA)	Active against OXA-type ESBL, No activity against OXA-type carbapenemase	Variable

IAI: Intraabdominal infection, UTI: Urinary tract infection, ESBL: Extended-spectrum beta-lactamase, FDA: Food and Drug Administration

is necessary in patients with a creatinine clearance of <50, and administering doses of antibiotic after hemodialysis is recommended[112].

In a study examining isolates from 121 patients with CRE bacteremia, 99% of the CRE isolates were susceptible to ceftazidime/avibactam. However, susceptibility was lower among KPC-3-producing strains[113]. In a study including bacteremia that assessed the *in vitro* susceptibility of different clinical isolates of *Pseudomonas* spp., the ceftazidime/avibactam susceptibility rates of MDR and XDR isolates were 78% and 80% and ceftolozane/tazobactam susceptibility rates were 89% and 80%, respectively[108].

In a multicenter prospective observational study comparing ceftazidime/avibactam with colistin for the treatment of CRE infections (46% of which were bloodstream infections), 30-day mortality was higher in the colistin group, and it was stated that ceftazidime/avibactam may be an alternative to colistin in the treatment of CRE[114]. A patient with KPC-3-producing *K. pneumoniae* bacteremia who showed no response to a meropenem + colistin + tigecycline combination was successfully treated with a combination of 4 hours of prolonged infusion of 2.5 grams of ceftazidime/avibactam + colistin + tigecycline[115]. Ceftolozane/tazobactam was used as a rescue therapy in 12 patients with sepsis due to MDR *P. aeruginosa*, with favorable outcomes in 9 of those patients[116].

Ceftaroline fosamil is the latest, fifth generation cephalosporin. It has broad-spectrum activity against Gram-positive bacteria, including MRSA. Its spectrum of activity includes methicillin-susceptible *S. aureus*, MRSA, VRSA, daptomycin- and linezolid-resistant *S. aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae*. It is also effective against Gram-negative bacteria such as *E. coli, K. pneumoniae, K. oxytoca,* and *Haemophilus influenzae*. However, its effect on *Pseudomonas* spp. and anaerobic bacteria is weak. It has Food and Drug Administration as well as European Medicines Agency indications for use in the treatment of community-acquired pneumonia and acute bacterial skin and skin structure infection[117].

New antibiotics are regarded as a treatment alternative for sepsis caused by MDR microorganisms. However, as with other beta-lactam antibiotics, prolonged infusion and combination therapies may improve success rates.

Non-antimicrobial Treatment

In addition to early antibiotic treatment, rapid correction of tissue hypoperfusion is the cornerstone of initial treatment of sepsis. Sepsis-induced tissue hypoperfusion causes decreased blood pressure and/or increased serum lactate levels, leading to acute organ dysfunction. For this reason, the 2016 revision of Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock stated that sepsis and septic shock are medical emergencies that require rapid initiation of treatment[79]. Administering 30 ml/kg of crystalloid fluids within the first 3 hours, especially in patients with high

lactate levels (≥4 mmol/L), is recommended to restore tissue perfusion[79]. A meta-analysis demonstrated that 6% HES (hydroxyethyl starch) was associated with higher mortality and need for renal replacement, compared to other solutions[118]. Therefore, crystalloids should be the first choice instead of colloid fluids such as HES. However, it is not clear which crystalloid fluid should be preferred. A 0.9% NaCl solution has higher Na (154 mmol/L) and Cl (154 mmol/L) levels compared to plasma. Thus, calling it normal or physiological saline is not completely accurate. The use of fluids with high Cl levels and those with a lower strong ion difference (SID) than plasma (0.9% NaCl SID: 0; plasma SID: 40 mmol/L) causes iatrogenic hyperchloremic metabolic acidosis[119]. In a study by Yunos et al.[120], the administration of a chloride-restrictive fluid was shown to reduce the development of acute kidney injury and the need for continuous renal replacement therapy. Zohou et al.[121] compared the low-chloride plasma-lyte with 0.9% NaCl solution in rats with experimentally induced sepsis and found an increase in acute kidney injury and mortality in rats treated with NaCl. However, sufficient clinical trials are needed to determine the safety and efficacy of balanced solutions in sepsis.

The addition of albumin is recommended when septic shock patients require a substantial amount of crystalloids. Xu et al.[122] reported in another meta-analysis that the use of albumin with crystalloid contributed to a reduction in 90-day mortality in patients with septic shock (n=3658) and a trend toward lower 90-day mortality among patients with sepsis (n=2180). Studies on this subject generally demonstrate that the use of albumin has a positive effect on 90-day mortality in septic shock, but indicate that this benefit is not as significant among sepsis patients[123,124]. The use of albumin is recommended (low-quality evidence, weak recommendation) in septic shock when there is a substantial increase in patients' crystalloid requirement[79].

Following protocol-based early intensive fluid resuscitation, it is still unclear how fluid balance should be managed. Fluid overload in sepsis has been shown to worsen respiratory function and prolong ventilator support (1.82 days) and stay in intensive care (1.88 days)[125]. This highlights the importance of evaluating fluid therapy. However, there is still uncertainty regarding how to evaluate fluid status. Assessment of fluid responsiveness should start with clinical findings (e.g. heart rate, blood pressure, arterial oxygen saturation, respiratory rate, urine output). The use of dynamic measurements based on passive leg raising or changes in intrathoracic pressure during mechanical ventilation (e.g. pulse pressure variation, stroke volume variation) is recommended over static measurements (e.g. central venous pressure, right or left heart pressures or volumes) for this assessment[79]. It has also been possible in recent years to assess the patients' hemodynamic status using bedside echocardiography.

A target MAP of 65 mmHg is recommended to correct hypoperfusion, decrease lactate levels, and sustain organ perfusion. If MAP cannot be maintained above 65 mmHg with intravenous fluid therapy, vasopressor support should be provided, with norepinephrine the first-line choice of vasopressor therapy. If response is insufficient, epinephrine or vasopressin (over 0.03 U/min) may be added. The use of low-dose dopamine for renal protection is strictly not recommended. It should only be used in selected patient groups such as those with severe bradycardia. A positive inotropic agent should be added if the patient has myocardial dysfunction or has MAP >65 mmHg and persistent hypoperfusion despite adequate fluid and vasopressor therapy. Dobutamine (20 mcg/kg/min) is considered to be the first-line inotrope in such cases. Hemodynamic monitoring via arterial catheter is more appropriate for patients requiring vasopressors.

In patients with septic shock, hydrocortisone at a dose of 200 mg/day is recommended if hemodynamic stability is not achieved with adequate fluid and vasopressor therapy[79,126]. Annane et al.[127] reported that the addition of fludrocortisone to hydrocortisone resulted in decreased 90-day mortality but also increased hyperglycemia in patients with septic shock. There are also studies reporting that adding vitamin C and thiamin to hydrocortisone prevented organ dysfunction and reduced mortality in patients with sepsis[128].

Adrenergic stimulation in patients with sepsis is associated with increased mortality and side effects. Morelli et al.[129] compared esmolol and standard therapy in septic shock patients requiring norepinephrine, and reported more favorable results in terms of heart rate control and increased stroke volume in the group that received esmolol, which resulted in reduced lactate levels, norepinephrine and fluid requirement, and mortality rates. However, there were methodological errors related to this study and it was determined that further research on this subject is required[130].

Regarding the use of blood products, erythrocyte suspension is recommended when hemoglobin level is below 7.0 g/dL. In the absence of hemorrhage or a planned invasive intervention, fresh frozen plasma should not be given to improve laboratory results. Prophylactic platelet suspension is recommended when platelet count is <10000/mm^3, or <20000/mm^3 in patients with hemorrhage risk. However, for patients who will undergo surgery or an invasive procedure or have active hemorrhage, platelet suspension should be given to increase platelet count >50000/mm^3[79].

Source Control

Source control involves measures to physically control contamination in order to eliminate the source of infection and

enable anatomic and functional restoration[131]. This includes abscess drainage, debridement of infected necrotic tissues, the removal of potentially infected devices, and the identification of sources of ongoing microbial contamination. In clinical practice, source control must be implemented immediately after the diagnosis of sepsis and septic shock. When source control is inadequate, patients do not improve despite rapid resuscitation and appropriate antimicrobial therapy[132]. The principles of source control in sepsis and septic shock management include the rapid identification of the specific focus of infection and assessing the adequacy of source control at the infectious site[133].

The effectiveness of source control depends on the site of infection, the patient's underlying diseases, and the nature of the source[134].

Intra-abdominal abscesses, gastrointestinal perforation, ischemic bowel or volvulus, cholangitis, cholecystitis, pyelonephritis associated with obstruction or abscess, necrotic soft tissue infections, other deep surface infections (empyema or septic arthritis), and implant infections are amenable to source control[135]. In septic shock with infective endocarditis, the removal of the infected tissue (valve, abscess, infected instrument, infected distant metastatic lesions) is among the cornerstones of treatment[136].

Source control should be achieved within 12 hours in sepsis and septic shock[137-142]. According to the Infectious Diseases Society of America guidelines, this can be extended to 24 hours if patients are stable, but source control is recommended as soon as possible in cases of diffuse peritonitis and septic shock[18].

The risks and benefits of the specific intervention should be weighed when selecting the most appropriate method for source control. Source control interventions can lead to certain complications such as hemorrhage or inadvertent organ injuries. In general, the least invasive and most effective method should be preferred for source control. Open surgical interventions should be done when other interventional methods are considered to be inadequate or not feasible. Percutaneous interventions may be preferable for patients in shock. Intravascular devices such as central venous catheters can be sources of sepsis or septic shock. Intravascular devices suspected to be septic sources should be removed immediately upon establishing another site for vascular access[143].

In patients with community-acquired infections, the lungs and urinary tract are the most common sources of infection. In addition, intra-abdominal infections (cholangitis, cholecystitis, diverticulitis), septic arthritis, endocarditis, and osteomyelitis should also be investigated. Hospital-acquired infections often occur due to disruption of the epithelial barrier. Infection frequently originates from intravascular catheters, endotracheal tubes (pneumonia and paranasal sinusitis), urinary catheters, and surgical wounds or other sites of traumatic injury. In general, in patients with sepsis, all intravascular and bladder catheters should be removed and placed at new sites if needed. Since medical treatment is usually adequate for infected thrombus, surgery is not necessary in most cases[144].

Conclusion

Sepsis is a syndrome characterized by organ failure resulting from an uncontrolled host inflammatory response against infection. Since early diagnosis and treatment significantly reduce mortality, an accurate and rapid diagnosis is vital. This has led to the creation of various diagnostic criteria over the years. Following rapid diagnosis, identification of the probable focus and causative microorganism has an important role in the selection of appropriate antimicrobial therapy.

The causative microorganism in sepsis varies depending on the infectious focus, the setting in which the infection was acquired, patient characteristics, and year. In order to identify the causative microorganism, cultures should be obtained immediately from the relevant sites and constant contact should be maintained with the microbiology laboratory. Rapid diagnostic methods for microbial identification as well as prognostic and predictive markers such as CRP and PCT should be employed according to availability in the healthcare institution. Antimicrobial therapy forms the basis of sepsis treatment. Appropriate initial empirical antimicrobial therapy increases the success of sepsis treatment. Initial empirical therapy should consist of one or more broad-spectrum agents with coverage against the possible microorganisms. Empirically initiated broad-spectrum therapy should be narrowed according to microbial culture and antibiotic susceptibility test results. Antimicrobial resistance greatly complicates the treatment of sepsis, leading to failure and increasing treatment costs. Therefore, the probable causative agent and its regional or hospital-specific resistance rates should be considered when selecting antibiotics to initiate therapy. Rapid correction of tissue hypoperfusion in addition to early antibiotic therapy is the cornerstone of initial therapy. Crystalloid fluids should be preferred to correct tissue hypoperfusion, and colloid fluids (particularly albumin), vasopressor support, and blood and blood product replacement should be provided depending on the patient's status. Despite early initiation of antimicrobial and non-antimicrobial therapies in the management of sepsis, the risk of mortality persists if source control is not achieved. Therefore, source control should be a top priority. Although definitions of sepsis may evolve, early diagnosis and treatment may be possible through education and awareness campaigns about sepsis. Early diagnosis and treatment can be realized with a multidisciplinary approach involving internal medicine, surgery, and laboratory staff.

Ethics

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Authorship Contributions

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