

SIRS and Septic Shock — Diagnostics and Therapy

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Systemic inflammatory response syndrome (SIRS) is an acute inflammatory pathology with a systemic body reaction. Triggers include trauma, surgery, inflammation, or infection. If pathogens from the source of the infection get into the bloodstream, sepsis or blood poisoning can occur. Sepsis and septic shock are the main causes of death of patients in the intensive care unit.



Definition of SIRS and Septic Shock

Activation of the cellular systems and release of cellular mediators during sepsis

When pathogens and their products move from the infection source into the bloodstream, life-threatening clinical symptoms can result; this is called sepsis. In sepsis, cascade systems and special cellular systems are activated, triggering the formation and release of cellular mediators. To create a base for clinical and epidemiologic studies, the symptoms of SIRS, sepsis, severe sepsis, and septic shock will be defined individually.

Systematic Inflammatory Response Syndrome

The first stage, which is independent of the triggering agent, is called **systemic inflammatory response syndrome (SIRS)**. For a diagnosis of SIRS, at least 2 of the following criteria must be met:

- Fever $> 38^{\circ}\text{C}$ or hypothermia $< 36^{\circ}\text{C}$ by rectal or invasive measuring
- Tachycardia with a heart rate > 90 beats/minute
- Tachypnea with a rate > 20 breaths/minute or hyperventilation with a partial pressure of carbon dioxide (pCO_2) < 33 mm Hg
- Leukocytosis, with white blood cell count $> 12,000/\text{mm}^3$, or leukopenia, with white blood cell count $< 4,000/\text{mm}^3$ or proportion of premature neutrophil granulocytes in the blood $> 10\%$

Additionally, there must be an **infectious agent** for the diagnosis of **sepsis**, which means that an infection has been identified by microbiological analysis or by means of clinical criteria.

Note: Sepsis occurs as soon as SIRS is triggered by an infection. Identifying the source of infection is sufficient to make a diagnosis of sepsis.

Acute organ failure during severe sepsis

Severe sepsis is diagnosed when at least one **acute organ failure** occurs. Acute organ failures include the following:

- Acute encephalopathy with limited vigilance, restlessness, and disorientation
- Arterial hypotension: systolic blood pressure < 90 mm Hg or mean arterial pressure (MAP) < 70 mm Hg for at least 1 hour, even with adequate hydration and after exclusion of other causes.
- Relative or absolute thrombocytopenia: a decrease in thrombocyte count of more than 30% within a 24-hour period or a thrombocyte count $< 100,000/\text{mm}^3$ (after bleeding has been excluded as the cause).
- Arterial hypoxemia: partial arterial pressure of oxygen (PaO_2) < 75 mm Hg in ambient air or the ratio of PaO_2 to fractional inspired oxygen (FiO_2) < 250 mm Hg with oxygen therapy (after heart and lung diseases have been excluded as the cause)
- Renal dysfunction: diuresis rate of < 0.5 mL/kg/h for at least 2 hours despite sufficient volume loading or an increase of serum creatinine level to 2 times the local creatinine limit.
- Metabolic acidosis with a base excess < -5 mmol/L or a lactate concentration > 1.5 times the locally normal reference range.

The septic shock

Septic shock is defined as sepsis with a systolic blood pressure of < 90 mm Hg that lasts for at least 2 hours, MAP < 70 mm Hg, or the necessity for vasopressin replacement to increase the blood pressure over these values. Hypotonia continues despite volume loading and cannot be explained by other causes.

The PIRO concept

The **PIRO concept** was proposed as a system for classifying sepsis and developing consensus criteria. The concept is analogous to the TNM staging used for malignant

tumors.

P: Predisposition

I: Infection

R: Inflammatory reaction

O: Organ dysfunction

Risk stratification of sepsis can take place based on the PIRO concept.

Further important terms include the following:

- **Bacteremia:** the presence of facultative pathogenic bacteria in the bloodstream without the participation of the circulation or other signs of intoxication.
- **Endotoxemia:** the presence of endotoxins in the blood without simultaneous bacteremia; lipopolysaccharides of the membranes of gram-negative bacteria function as endotoxins
- **Septicemia:** infection of the entire organism by microorganisms, endotoxins, toxins, or pyrogens
- **Septic-toxic shock:** An acute reduction of the oxygen supply of vital organs with functional and structural changes that can lead to multiorgan failure within a short period.

Epidemiology of SIRS and Septic Shock

Increasing incidence of sepsis

The average incidence of sepsis in the European region is **5 cases per 1,000 hospital patients** and is increasing steadily. Reasons for this increasing incidence include more invasive examination techniques, which present an entry for pathogens, and the increasing survival rates of patients with chronic diseases such as malignant tumors, kidney diseases, and HIV.

Etiology of SIRS and Septic Shock

Causes of SIRS include both infectious and noninfectious conditions, surgical procedures, trauma, medications, and therapies. Generalized inflammatory reactions caused by SIRS fall into 2 categories: **pathogen-associated molecular patterns** (PAMPs) and **damage-associated molecular patterns** (DAMPs).

- **PAMPs** are caused by the lysis of foreign cells, which releases molecules intrinsic to the cells' structure into the circulation.
- **DAMPs** arise when cellular injury occurs at rates that overwhelm local clearance mechanisms. Thus, generalized bacteremia, severe pneumonia (viral or bacterial), severe trauma with tissue injury, and pancreatitis all share common inflammatory activation pathways.

Sepsis syndrome occurs when there is **predisposing reduced resistance** from general infection, trauma or large operations, intoxications, chemotherapy, splenectomy (ie overwhelming post-splenectomy infection [OPSI]), or amicrobial inflammation.

Before the use of antibiotics, streptococci were considered the most important pathogens

in septic processes. Today, there are more **gram-negative bacteria and staphylococci** because of intensive care units' long-term use of antibiotics, which function against Gram-negative bacteria and result in resistant strains.

Escherichia coli is now the most frequently found bacterium, isolated from blood cultures of 25% of septic patients. *Staphylococcus aureus* (20%); *Staphylococcus epidermis* (8%); and *Enterococcus*, *Klebsiella*, and *Pseudomonas* species are frequent as well. The **most frequent infection sources** are **peritonitis, pneumonia, meningitis, and surgery**. In the case of intensive care patients, bacteria can also get into the body by other means, such as intravenous and intra-arterial catheters, peritoneal dialysis, and ventilation tubes.

Pathophysiology of SIRS and Septic Shock

Hypodynamic stage of sepsis

Lipopolysaccharides (LPS) are embedded in the outer membrane of gram-negative bacteria. LPS, which has proinflammatory properties, is secreted into the circulation after a bactericide antibiotics or a massive increase in bacteria.

In early sepsis, before treatment, there is often a **hypodynamic stage**. This phase is defined by **hypotonia, low heart rate volume, and an increased systemic resistance**; it is also called **cold shock**. At this stage, volume substitution is essential because circulation shock is the cause of approximately 40% of deaths during sepsis.

Note: The untreated early stage of sepsis (hypodynamic form) should not occur because adequate volume substitution must always take place.

Hypodynamic initial stage of sepsis

With the help of mediators, arterial and venous vasodilatation is consequently triggered, which leads to decreased systemic vascular resistance, venous pooling, and system arterial hypotension caused by the relative lack of intravascular volume. This is referred to as the **hyperdynamic initial stage**.

If capillary leakage syndrome also occurs because of increased vascular permeability there is a complete lack of volume. **Increased heart rate and volume** are characteristic of this stage, which can partially compensate for the hypovolemia. The blood is only to some extent depleted of O₂, and the mixed venous O₂ saturation (SvO₂) is high (>80%) due to this hypocirculation.

Additionally, and already at this stage, there is decreased myocardial contractility, which is shown by the fact that the measured increase in heart rate does not correlate with the range of the reduced systemic vascular resistance. The reasons for this include mediators such as tumor necrosis factor- α and endotoxins. The constantly increased plasma catecholamine levels and disturbed myocardial microcirculation lead to a reduced sensitivity of the cardiac β -receptors. The relative heart insufficiency during septic syndrome is also called **acute septic cardiomyopathy**.

Hypodynamic shock phase of sepsis

In some patients, the hyper-circulation turns at a later point into a **hypodynamic shock phase** as an expression of the decompensation of the endogenous mechanisms that

regulate homeostasis. The heart rate and volume decrease again and the resistance increases, but, by means of a sufficient volume substitution, the hyperdynamic circulation constellation is maintained in most patients—often, even until the final stage.

Functional restriction of vital organs or organ failure can take place even in the hyperdynamic stage. The blood gathers in the organs due to a failure of arteriolar vasomotion, which is the rhythmic contraction and dilatation of the arterioles. Therefore, the arteriovenous shunts open and, thus, the organs are increasingly flooded, causing **tissue hypoxia** and nutritive disturbances.

Clinical studies have shown that systemic consumption of oxygen is decreased, whereas the availability of oxygen is generally increased as a result of the septic hypermetabolism; however, a sufficient cellular oxygenation cannot be assumed if there are low arteriovenous oxygen saturation difference (AVDO₂) values because there is an oxygen use disturbance on a mitochondrial level with septic syndrome. The affinity of hemoglobin for oxygen is increased as well; thus, the oxygen can reach the tissue only in a complicated way.

The **core problem of sepsis syndrome is, therefore, the microcirculation disturbance**, which remains despite the counter-regulation of the circulation. If not treated, the tissue hypoxia can lead to single or multiorgan failure, which is associated with lethality of 50%–80%. **Chronologically, the lungs fail first, followed by the kidneys and the liver.**

Diagnostics of SIRS and Septic Shock

Clinical parameters and sepsis signs

At first, sepsis is marked by a pathogen invasion. There is an **acute decline in general condition, fever**, and—in approximately one-third of patients, **ague**. **Leukocytes** are found in the blood, and leukopenia is possible as well. Differentiation from SIRS is possible only by determining a sepsis or infection source.

Pathogenesis	Symptom
Germ invasion	Fever, ague, bacteremia, red, warm, wet skin or pale, cold, wet skin, petechial bleeding.
Hemodynamics	Tachycardia, hypotension (especially the diastolic value).
Coagulation	Fall of thrombocytes, coagulation factors decrease.
Organ dysfunction	Tachypnea (PO ₂ and PCO ₂ decrease), restlessness, confusion, kidney and liver insufficiency, encephalopathy, respiratory insufficiency, myocardial insufficiency.

Common clinical parameters, such as body temperature, numbers of leukocytes and thrombocytes, and parameters of the coagulation system (quick, partial thromboplastin time) often cannot properly represent the range of the complexity of the inflammation. Therefore, more laboratory values must be determined. These include **interleukin (IL) 6 and IL-8 as proinflammatory mediators**.

Lipopolysaccharide binding protein (LBP) and C-reactive protein (CRP) can be considered as well, although **procalcitonin** is more often considered than CRP because test results are highly positive for procalcitonin only during bacterial infection, whereas

CRP also increases with other causes of SIRS, such as pancreatitis, burns, and serious trauma. Additionally, procalcitonin is a more significant predictor of the severity of the infection.

The neurohumoral markers **ANP** (atrial natriuretic peptide) and **BNP/NT pro BNP** (brain natriuretic peptide) can be increased as well in patients with septic shock, and the increase BNP indicates a cardiac dysfunction.

Lactate acidosis is a sign for the tissue hypoxia.

Note: Do not underestimate the usefulness of standard parameters such as quick, PTT, and numbers of leukocytes and thrombocytes in daily clinical work.

Microbiological diagnostics

Although **blood culture test results** are positive in only approximately 12%–20% of bacteremia cases, blood cultures are essential for detecting pathogens when there is suspicion of sepsis. They should be taken under sterile circumstances in the case of an increased fever (regularly in the case of a temperature above 38.5°C) and before the start of antibiotics.

An aerobe and an anaerobe culture flask should each be filled with approximately 10 mL of blood, and the standard is to fill a pair of blood culture flasks from each of 3 different veins (or, for example, from a ZVK or port and periphery veins). If the vascular circumstances or the centralization are unfavorable, the vena or arteria femoralis can be punctured as well. If the patient is already receiving antibiotic therapy, cultures should be taken during the therapy trough level. For this, there are special blood culture flasks that contain exchange resins, which bind the antibiotics and make them ineffective.

If necessary based on the clinical picture, more **samples, such as urine, liquor, or bronchial secretions**, should be taken and examined microbiologically.

Note: The more often tests are performed, the greater the chance of determining the source of the disease. For a thorough search, physical examination, history, and imaging diagnostics are necessary.

Clinical result	Possible cause of sepsis
Vitium-typical sound during cardiac listening.	Endocarditis
Pulmonary rhonchus/weakened auscultation finding during the examination of the lungs.	Pneumonia , pleuraempyema
Abdominal pressure pain/flank pain.	Pancreatitis , cholecystitis, pyelonephritis
Abdominal resistance tension.	Peritonitis, pancreatitis
Meningism.	Meningitis, encephalitis
Redness, overheating, painful skin.	Phlegms, abscess

Monitoring

For the monitoring of patients with sepsis in the intensive care unit, basic monitoring is recommended. For patients in whom blood flow is difficult to control, extended monitoring is recommended. This extended hemodynamic monitoring includes the **transthoracic or transesophageal echocardiography** for recording the left ventricular pump function.

A **pulmonary artery catheter** should be used as well to determine the heart rate and

volume and the systemic vascular resistance; the Pulse Index Contour Continuous Cardiac Output system (**PiCCO system**) is especially appropriate. This allows for measurement of the heart rate volume, extravascular lung water, intrathoracic blood volume, and systemic vascular resistance by using a combination of arterial pulse contour analysis and a transpulmonary indicator dilution process. According to the sepsis guiding lines of Dellinger et al. (2008) (Survival Sepsis Campaign), **oxygen saturation** plays an especially important role as a monitoring parameter.

Complications

Complications vary based on underlying etiology. Routine prophylaxis, including deep vein thrombosis (DVT) and stress ulcer prophylaxis, should be initiated when clinically indicated in severely ill, bedridden patients, especially if they require mechanical ventilation. Long-term antibiotics, when clinically indicated, should have as narrow a spectrum as possible to limit the potential for superinfection. Unnecessary vascular catheters and Foley catheters should be removed as soon as possible. Potential complications include the following:

- Respiratory failure, acute respiratory distress syndrome (ARDS), and nosocomial pneumonia
- Renal failure
- Gastrointestinal (GI) bleeding and stress gastritis
- Anemia
- DVT
- Intravenous catheter-related bacteremia
- Electrolyte abnormalities
- Hyperglycemia
- [Disseminated intravascular coagulation](#) (DIC)

Treatment of SIRS and Septic Shock

The basis of a successful treatment for sepsis is the detection of the source and its removal; hence, abscesses must be drained, and infected foreign matter must be removed. If it is assumed that a central venous catheter or port is the focus of infection, this should be confirmed. If the blood culture of the central catheter becomes significant before the culture result of a periphery vein is positive, an infection of the ZVK can be assumed. In the case of infections of an endoprosthesis, the endoprosthesis must be surgically removed and, if necessary, replaced by a spacer containing antibiotics.

Antimicrobial therapy

Broad-spectrum antibiotics

Antibiotic therapy must be adjusted to the source and the expected range of pathogens. If the source of the sepsis is not known, the antibiotics must cover all gram-negative and gram-positive bacteria, as well as anaerobes.

A **combination of wide-spectrum** penicillin-like piperacillin or third-generation **cephalosporin** (e.g., **cefotaxime with an aminoglycoside such as gentamicin**) often is used.

Gram-negative coverage with cefepime, piperacillin-tazobactam, carbapenem (imipenem, meropenem, or doripenem), or a quinolone is reasonable. The therapy should begin

within the first hour of detection of severe sepsis with intravenous administration of antibiotics and should be continued for 7–10 days.

With the increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), **vancomycin** or another anti-MRSA therapy should be considered.

Penicillin allergy

A quinolone or aztreonam is a reasonable choice for gram-negative coverage in patients with a penicillin allergy. If aztreonam is used, gram-positive coverage (with an agent such as vancomycin) should be initiated as well.

Skin Infection

Three antibiotics, [oritavancin](#), [dalbavancin](#), and [tedizolid](#) can be used for the treatment of acute bacterial skin infections. These agents are active against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus anginosus*.

Antiviral and antifungal therapy

Antifungal therapy with fluconazole or an echinocandin can be considered for patients who have already been treated with antibiotics, those who are neutropenic, those who are receiving total parenteral nutrition (TPN), or those who have central venous access in place.

If the septic course of the disease persists despite the administration of antibiotics, a secondary infection, infected foreign matter, infected thrombosis, and abscesses must be excluded. There could also be a so-called **drug fever** caused by the medication.

Insulin therapy

The **intensive insulin therapy** to reach a normoglycaemia in the form **sepsis prevention** offers in the case of post-operatively ventilated intensive patients surprisingly positive results. Nevertheless, the use is controversial, even in the case of septic patients.

Immune globulins

The general administration of immune globulins is not recommended because there are no proven prospective studies concerning this issue. The administration of high doses of glucocorticoids does not improve the survival rate of patients who suffer from sepsis. In contrast, a lower dose of hydrocortisone combined with catecholamines can buffer a disturbance of the hypothalamus-pituitary-adrenal cortex axis, which often occurs during sepsis.

Oxygen supplement

In the case of respiratory insufficiency, **endotracheal intubation** and ventilation can become necessary. In the approximately 40% of patients with severe sepsis in whom **acute respiratory distress syndrome (ARDS)** occurs, ventilation **with low tidal volume** for **lung protection** should take place if hypercapnia can be tolerated.

To prevent lung collapse, a low positive end-expiratory pressure (PEEP) can be used. To avoid ventilation-induced pneumonia, patients should rest with the head of the bed raised by 45°. Providing too much oxygen to a patient with severe chronic obstructive

pulmonary disease (COPD) should be avoided because it can depress the respiratory drive.

In tissue hypoxia, **erythrocyte preparations** are to be transfused when hemoglobin values are less than 7 g/dL. The correction of the coagulation factors in the case of a lack is recommended as well.

Supportive therapy for the heart

In addition to treating the cause of sepsis, quick introduction of supportive therapy for the heart, circulation, and organs is a significant prognostic factor. With the help of **early-goal-directed therapy, suspicion of sepsis** should lead to **immediate volume therapy**. A study showed that lethality could be decreased by 16% compared with conventional intensive therapy.

Vasopressors such as **terlipressin** can also be used in the case circulation failure that is resistant to therapy despite high doses of noradrenaline. The administration of dobutamine is shown in the case of patients with myocardial dysfunction.

For filling intravascular volume, **colloids** or **crystalloids** are used. A phase of the steady state with a hypercirculatory warm shock can result from the administration of volume. Additionally, catecholamine therapy **with norepinephrine** should take place.

Note: The sepsis guidelines require that hemodynamic goals are reached within the first 6 hours after diagnosis.

Prognosis of SIRS and Septic Shock

The time period from the start of disease to the point of therapy initiation or acute treatment has a significant influence on the course and prognosis of sepsis. The first 24 hours from the start of the disease are the so-called **golden hours**. Similar to other emergency clinical disease pictures (e.g., myocardial infarct or apoplexy), the lethal course of sepsis can be prevented only by immediate diagnosis and the consecutive introduction of therapy.

One of the main reasons for the unchanged high mortality rate of severe sepsis and septic shock is late diagnosis and the resulting delay of therapy. The **MEDS score (Mortality in Emergency Department Sepsis Score)** was developed for patients in the emergency department with suspected systemic infection. Its aim is to identify **predictors of increased mortality** already present in the initial phase of hospital treatment. It is also important for identifying patients whose clinical characteristics are unremarkable but already show a slow septic course with global tissue hypoxia.

MEDS score according to Shapiro et al. (2003): Mortality with a MEDS score of 5–7 points is 3.3%; it increases by 10 times to 31.6% with a score of 13 or more points. Shapiro et al. evaluated mortality in patients with suspected infection in the emergency department and found the following in-hospital mortality rates :

1.	Disease in the terminal stage (life expectation < 30 days)	6 points
2.	Respiratory insufficiency (tachypnea, low O2 saturation, high need of O2)	3 points

3.	Septic shock (constant hypotonia with syst. RR < 90 mmHg after an initial fluid challenge of 20 - ml/kg bodyweight)	3 points
4.	Thrombocytes < 150.000/mm ³	3 points
5.	Age > 65 Jahre	3 points
6.	Infection of the lower respiratory tract	2 points
7.	Home residents	2 points
8.	Reduced mental status	2 points

- Suspected infection without SIRS: 2.1%
- Sepsis : 1.3%
- Severe sepsis : 9.2%
- Septic shock : 28%

Apart from the mortality predictions of the MEDS score, an **increased lactate serum concentration** and an **increased mixed venous oxygen saturation** showing a lack of tissue extraction are guiding parameters of early disturbed tissue oxygenation.

The **mortality** of sepsis is **approximately 28%**. It especially depends on the patient's age: mortality is approximately 10% in children but 38% in people older than 85 years.

Review Questions

The correct answers can be found below the references.

1. What is not a diagnosis criterium of SIRS?

- A. Fever > 38,5 °C or hypothermia < 36 °C
- B. Heart rate > 90/min
- C. Tachypnea > 20/min
- D. Leukocytosis > 12.000/mm³ or leukopenia < 4.000/mm³ or > 10 % of immature neutrophil granulocytes in the blood
- E. Proven infection as a cause

2. A 66-year-old patient received a total replacement of the left hip due to coxarthrosis 5 days ago. Now, the patient has a high temperature of 39.2°C and is hemodynamically unstable. The surgical wound is heavily reddened and hyperthermic. You assume an infection and take multiple aerobic and anaerobic blood cultures and wound swabs. What is consequently necessary for the successful treatment of sepsis?

- A. Circulation stabilization by means of volume substitution therapy and norepinephrine.
- B. Antibiotherapy with wide-spectrum antibiotics as piperacillin in combination with gentamicin.
- C. Surgical cleaning with wound debris, jet lavage, and removal of the infected endoprosthesis.
- D. Intensified insulin therapy.
- E. Administering of immune globulins, activated protein C, and hydrocortisone.

3. What is not part of the predictors of the MEDS score that accompany an elevated mortality rate during sepsis?

- A. Age > 65 years
- B. Thrombocytes < 150.000/mm³

- C. Home residents
- D. Age < 5 years
- E. Respiratory insufficiency

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[AWMF-Leitlinie Sepsis](#)

Correct answers: 1E, 2C, 3D

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Notes