SIRS and Septic Shock — Diagnostics and Therapy

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The systemic inflammatory response syndrome is an acute inflammatory pathology with a systemic body reaction. Triggers include traumata, big operations, inflammations or, for example, infections. If pathological germs get from one source of infection into the bloodstream, a sepsis or blood poisoning occurs. Sepsis and septic shock are the main causes of death on the Intensive Care Unit.

Definition of SIRS and Septic Shock

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

All life-threatening clinical symptoms which occur due to a reaction to pathogen germs and its products which get from the infection source into the bloodstream are defined as sepsis. Due to these, cascade systems and special cellular systems are activated and the formation and release of cellular mediators are triggered.

In order to create a base for clinical and epidemiological studies, the symptoms SIRS,
sepsis, severe sepsis and septic shock are defined coherently.

**Systematic Inflammatory Response Syndrome**

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

- Fever > 38° C or hypothermia < 36 °C in the rectal or invasive measuring.
- Tachycardia with a heart rate > 90/min.
- Tachypnea with a rate > 20/min or hyperventilation with a PCO2 < 33 mmHg.
- Leukocytosis with > 12.000/mm³ or leukopenia < 4.000/mm³ or > 10 % of premature neutrophil granulocytes in the blood.

Additionally, there must be an **infectiological genesis** for the diagnosis of **sepsis** which means that an infection has to be found in the microbiological proof or by means of clinical criteria.

**Note:** As soon as a SIRS is triggered by an infection, there is sepsis. It is enough to consider an infection as a cause.

**Acute organ failure during severe sepsis**

**Severe sepsis** is every sepsis where at least one **acute organ failure** occurs. Acute organ failures include:

- Acute encephalopathy with limited vigilance, restlessness, and disorientation.
- Arterial hypotension with systolic blood pressure > 90 mmHg or MAP < 70 mmHg for at least 1 hour, even with adequate hydration and exclusion of other shock causes.
- Relative or absolute thrombocytopenia, thus a decrease of the thrombocytes of more than 30% within a period of 24 hours or decrease of thrombocytes < 100.00/mm³ (a thrombocytopenia due to bleeding is excluded).
- Arterial hypoxemia with PaO2 < 75 mmHg in ambient air or a PaO2/FiO2 relation of < 250 mmHg with oxygen therapy (heart and lung diseases as the cause for the hypoxemia are excluded).
- Renal dysfunction with a diuresis rate of < 0.5 ml/kg/h for at least 2 hours despite sufficient volume loading, or an increase of the serum creatinine twice above the local creatine limit.
- Metabolic acidosis with a base excess < -5 mmol/l or a lactate concentration of > 1,5 times above the locally normal reference range.

**The septic shock**

The septic shock is defined as a sepsis with a systolic blood pressure of < 90 mmHg which lasts at least for 2 hours or MAP < 70 mmHg or vasopressin replacement to increase the blood pressure over the mentioned values. The hypotonia continues despite a volume loading and cannot be explained by other forms of shocks.

**The PIRO concept**

The **PIRO concept** is an attempt to develop the consensus criteria for sepsis mentioned above; therefore, a classification of the sepsis in analogy to the TNM classification of malign tumors was proposed.
P Predisposition
I Infection
R Inflammatory reaction
O Organ dysfunction

A risk stratification of sepsis can take place based on this division.

Further important terms are:

- **Bacteremia** includes the presence of facultative pathogen bacteria in the bloodstream without the participation of the circulation or other signs of intoxication.
- **Endotoxemia** is defined as the presence of endotoxins in the blood, also without simultaneous bacteremia. Lipopolysaccharides of the membrane of Gram-negative bacteria function as endotoxins.
- **Septicemia** is the intoxication of the entire organism by microorganisms, endotoxins, toxins, and pyrogens.
- If there is an acute reduction of the O2-supply of vital organs with functional and structural changes, it is referred to as a **septic-toxic shock**. It can lead within a short period of a multi-organ failure.

### Epidemiology of SIRS and Septic Shock

#### Increasing incidence of sepsis

The incidence of sepsis is stated on average in the European region with 5 diseases per 1,000 hospital patients and increases steadily. The reason for the increasing incidence includes more invasive examination techniques which present an entry for pathogen germs, as well as the increase of the survival rate of patients with chronic diseases such as malignant tumors, kidney diseases, and HIV.

#### Etiology of SIRS and Septic Shock

The etiology of SIRS includes infectious and non-infectious conditions, surgical procedures, trauma, medications, and therapies. Generalized inflammatory reaction caused by SIRS fall into two categories: PAMPs and DAMPs.

- **PAMPs (Pathogen-associated molecular patterns):** These are present when infection of foreign cell lysis releases these foreign molecules intrinsic to their structure into the circulation.
- **DAMPs (damage-associated molecular patterns)** arise when cellular injury occurs at rates that overwhelm local clearance mechanisms. Thus, it can be seen that generalized bacteremia, severe pneumonia (viral or bacterial), severe trauma with tissue injury, and pancreatitis all share common inflammatory activation pathways.

The sepsis syndrome occurs based on a **predisposing reduced resistance** during diseases as general infection, trauma and large operations, intoxications, chemotherapy, after a splenectomy (OPSI = overwhelming post-splenectomy infection) and amicrobial inflammations.

Before the use of antibiotics, streptococci were considered as the most important pathogens of septic processes. Nowadays, there are more **Gram-negative bacteria and staphylococci** which can be related to the long-term use of antibiotics in intensive care.
which function against Gram-negative bacteria and the resulting developments of resistance.

With 25 %, *Escherichia coli* is nowadays the most frequent bacterium isolated from blood cultures of septic patients. *Staphylococcus aureus* with 20%, *Staphylococcus epidermis* (8%), enterococci, *Klebsiella*, and *Pseudomonas* are frequent as well. The most frequent infection sources are *peritonitis, pneumonia, meningitis*, and operation areas. In the case of intensive care patients, bacteria can also get into the body through other entries as intravenous and intra-arterial catheters, peritoneal dialysis and ventilation tubes.

Pathophysiology of SIRS and Septic Shock

Hypodynamic stage of sepsis

*Lipopolysaccharide* (LPS), is embedded in the outer membrane of Gram-negative bacteria. The LPS and hence pro-inflammatory potential are secreted into the circulation after a bactericide antibiosis or a massive increase in bacteria.

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

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

Hypodynamic initial stage of sepsis

With the help of mediators, an arterial and venous vasodilatation is consequently triggered which leads to a decreased systemic vascular resistance and venous pooling to system-arterial hypotension with the relatively intravascular lack of volume. It is referred to as a hyperdynamic initial stage.

If a capillary leakage syndrome with an increased vascular permeability joins in, it is a complete lack of volume. An increased heart rate volume is characteristic for this stage, whereby the hypovolemia can be partially compensated. The blood is only to some extent depleted with O2 and the mixed venous O2-saturation is high (SvO2 > 80 %) due to this hypocirculation.

Additionally, and already at this stage, there is a lowered myocardial contractility which is shown by the fact that the measured increase of the heart rate volume does not correlate with the range of the reduced systemic vascular resistance. The reason for this includes different mediators as TNF-α and endotoxins. The constantly increased plasma catecholamine levels, as well as the disturbed myocardial microcirculation, lead to a reduced sensitivity of the cardiac β-receptors. The relative heart insufficiency during the septic syndrome is also called acute septic cardiomyopathy.

Hypodynamic shock phase of sepsis

In the case of some patients, the hypercirculation turns at a later point into a hypodynamic shock phase as an expression of a decompensation of the endogenous
mechanisms which regulate the homeostasis. The heart rate volume decreases again, and the resistance increases, but, by means of a sufficient volume substitution, the hyperdynamic circulation constellation is maintained in the case of most patients; in most cases even until the final stage.

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

Clinical studies showed proof that the systemic consumption of oxygen is decreased, whereas the offer of oxygen is generally increased as a result of the septic hypermetabolism, but one cannot assume a sufficient cellular oxygenation if there are low avDO2-values because there is an oxygen utilization disturbance on a mitochondrial level during a septic syndrome. The affinity of the hemoglobin for oxygen is increased as well, thus the oxygen can only reach the tissue in a complicated way.

The core problem of the sepsis syndrome is, therefore, the microcirculation disturbance which remains despite the counter-regulation of the circulation. If not treated, the tissue hypoxia leads to a single or multi-organ failure which is socialized with a lethality of 50—80%. In the chronological order of the MOF (multi-organ failure), the lung comes first, followed by the kidney and the liver.

**Diagnostics of SIRS and Septic Shock**

**Clinical parameters and sepsis signs**

In the beginning, the image of sepsis is marked by a germ invasion. An acute decline of the general condition with fever and, in the case of about a third of the patients, ague takes place. In the blood, leukocytes are found, whereas a leukopenia is primarily possible as well. The differentiation in relation to the SIRS is only possible by means of the proof of a sepsis source or an infection source.

<table>
<thead>
<tr>
<th>Pathogenesis</th>
<th>Symptom</th>
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<tbody>
<tr>
<td>Germ invasion</td>
<td>Fever, ague, bacteremia, red, warm, wet skin or pale, cold, wet skin, petechial bleeding.</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>Tachycardia, hypotension (especially the diastolic value).</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Fall of thrombocytes, coagulation factors decrease.</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>Tachypnea (PO2 and PCO2 decrease), restlessness, confusion, kidney and liver insufficiency, encephalopathy, respiratory insufficiency, myocardial insufficiency.</td>
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The common clinical parameters as the body temperature, number of leukocytes and thrombocytes and parameters of the coagulation system (quick, PTT) often cannot represent properly the range of the complexity of the inflammatory occurrence. That is the reason why more laboratory parameters must be determined. These include **IL-6 and IL-8 as pro-inflammatory mediators**.

The lipopolysaccharide binding protein (LBP) and the c-reactive protein (CRP) can be considered as well, whereas procalcitonin is more often considered than CRP as it is
only highly positive during a bacterial infection, while the CRP also increases due to other causes of SIRS as pancreatitis, burns and big traumata. Additionally, procalcitonin allows for a more significant predictor of the severity of the infection.

The neurohumoral markers ANP (atrial natriuretic peptide) and BNP/NT per BNB (brain natriuretic peptide) can be increased as well in the case of patients with septic shock, whereas the increase BNB shows a cardiac dysfunction.

The lactate acidosis is a sign for the tissue hypoxia.

**Note:** Don’t underestimate standard parameters as quick, PTT, number of leukocytes and thrombocytes during the daily clinical work as they work as indicators.

**Microbiological diagnostics**

Although blood cultures are only positive in about 12—20% of the bacteremia, they are essential for the proof of germs in the case of the suspicion of sepsis. They should be taken in the case of an increase of fever (regularly in the case of a temperature above 38.5 °C) and before the start of the antibiotics under sterile circumstances.

The minimum is to fill an aerobe and an anaerobe culture flask with about 10 ml of blood, whereby the standard is to take 3 pairs of blood culture flasks from different veins (or for example from a ZVK or port and periphery veins). If the vascular circumstances or the centralisation are unfavorable, the V. or A. femoralis can be punctuated as well. If the patient is already under an antibiotic therapy, cultures should be taken during the therapy trough level. For this cause, there are special blood culture flasks which contain exchange resins which bind the antibiotics and make them ineffective.

According to the clinical picture, more tests like urine, liquor or bronchial secretion should be taken and examined microbiologically.

**Note:** The more often tests are taken, the bigger the chance is to proof sources of diseases.

For the focus search, body examination, anamnesis and imaging diagnostics are necessary.

<table>
<thead>
<tr>
<th>Clinical result</th>
<th>Possible cause of sepsis</th>
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<tbody>
<tr>
<td>Vitium-typical sound during cardiac listening.</td>
<td><strong>Endocarditis</strong></td>
</tr>
<tr>
<td>Pulmonary rhonchus/weakened auscultation finding during the examination of the lungs.</td>
<td><strong>Pneumonia</strong>, pleuraempyema</td>
</tr>
<tr>
<td>Abdominal pressure pain/flank pain.</td>
<td><strong>Pancreatitis</strong>, dholecystitis, pyelonephritis</td>
</tr>
<tr>
<td>Abdominal resistance tension.</td>
<td><strong>Peritonitis</strong>, pancreatitis</td>
</tr>
<tr>
<td>Meningism.</td>
<td><strong>Meningitis</strong>, encephalitis</td>
</tr>
<tr>
<td>Redness, overheating, painful skin.</td>
<td><strong>Phlegms</strong>, abscess</td>
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**Monitoring**

For the monitoring of septic patients on the Intensive Care Unit, the basic monitoring, and an extended monitoring, especially in the case of patients who are hard to control in a hemodynamic manner, are recommended. The extended hemodynamic monitoring includes the **transthoracic or transoesophageal echocardiography** for the recording of the left ventricular pump function.
A pulmonary artery catheter is meant to be used as well for the determination of the heart rate volume and the systemic vascular resistance; especially, PiCCO systems are appropriate. They allow for a measurement of the heart rate volume, the extravascular lung water, the intrathoracic blood volume and the systemic vascular resistance by using a combination of arterial pulse contour analysis and transpulmonary indicator dilution process. According to the sepsis guiding lines of Dellinger et al. 2008 (Survival Sepsis Campaign), especially the oxygen saturation as a monitoring parameter plays an important role.

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 bed-ridden patients, especially if they require mechanical ventilation. Long-term antibiotics, when clinically indicated, should be as narrow 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 base of a successful therapy of the sepsis is the detection of the source and its removal; hence, abscesses must be drained and infected foreign matters must be removed. If it is assumed that a central venous catheter or port is infected and the focus, the time is used until positivity is accomplished. If the blood culture of the central catheter becomes significantly before the culture of a periphery vein positive, an infection of the ZVK can be assumed. In the case of infections of the endoprosthesis, these must be removed in another surgery and, if necessary, replaced by a spacer containing antibiotics.

Antimicrobial therapy

Broad-spectrum antibiotics

The antibiotic therapy must be adjusted to the source and the expected range of germs. If the source of the sepsis is not known, the antibiosis must cover all Gram-negative and positive germs, as well as anaerobes.

A combination of wide-spectrum penicillin-like piperacillin or cephalosporin of the third generation (as cefotaxime with an aminoglycoside like gentamycin) often takes place. 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 the detection of the severe sepsis with an intravenous administration of antibiotics and be continued for 7—10 days.

With the increasing prevalence of methicillin-resistant Staphylococcus aureus (MRSA) in the community, 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 in patients who have already been treated with antibiotics, patients who are neutropenic, patients who are receiving total parenteral nutrition (TPN), or patients 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, an infected thrombosis, and abscesses must be excluded. It can also be a so-called drug fever under 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 as there are no proven prospective studies concerning this issue. The administration of highly dosed glucocorticoids does not improve the survival rate of patients who suffer from sepsis. In contrast, a lower dosed 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 a respiratory insufficiency, an endotracheal intubation and ventilation can become necessary in a supportive manner. As in the case of about 40% of patients with severe sepsis, and acute respiratory distress syndrome (ARDS) occurs, ventilation for the lung protection with low tidal volume should take place, a hypercapnia can be tolerated.

To prevent a lung collapse, a minimum of positively end-expiratory pressure (PEEP) can
be used. To avoid ventilation-induced pneumonia, the patients should be rested with the head part of the bed raised by 45°. Providing too much oxygen in a patient with severe chronic obstructive pulmonary disease (COPD) should be avoided because it can depress the respiratory drive.

Due to a tissue hypoxia, **erythrocytes preparations** are to be transfused already with hemoglobin values under 7 g/dl. The correction of the coagulation factors in the case of a lack is recommended as well.

### Supportive therapy for the heart

Apart from the causal therapy means, the quick introduction of the supportive therapy which supports the heart, the circulation and the organs is the significant prognosis factor. With the help of the **early-goal-directed-therapy**, a **suspicion of sepsis** leads to the **immediate volume therapy**. A study proved that the lethality could be decreased by 16% in comparison to a conventional intensive therapy.

Vaspressors as **terlipressin** can be used additionally in the case of therapy-resistant circulation failure despite high doses of noradrenaline. The administration of dobutamine is shown in the case of patients with myocardial dysfunction.

For the filling of the 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, a catecholamine therapy with **norepinephrine** should take place.

**Note:** The sepsis guideline requires that, within the first 6 hours after the diagnosis, the reach of the hemodynamic goal corridors.

### Prognosis of SIRS and Septic Shock

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

One of the main reasons for the unchanged high lethality rate of severe sepsis and septic shock is the late diagnosis and the resulting delay of therapy in the case of already-hospitalized patients, as well as in the case of patients already accommodated in the emergency room.

The **MEDS score** *(Mortality-in-Emergency-Department-Sepsis-Score)* was developed for patients in the emergency room with a suspicion of a systemic infection. Its aim is to identify **predictors of an increased lethality** already in the initial phase of hospital treatment. It is also important, for example, to select patients who are still unobtrusive in a clinical manner but already show a slow septic course with global tissue hypoxia.

**MEDS score according to Shapiro et al. 2003:**

<table>
<thead>
<tr>
<th></th>
<th>Disease in the terminal stage (life expectation &lt; 30 days)</th>
<th>6 points</th>
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<tr>
<td>2.</td>
<td>Respiratory insufficiency (tachypnea, low O2 saturation, high need of O2)</td>
<td>3 points</td>
</tr>
</tbody>
</table>

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/mm³ 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

While the lethality with 5—7 points amounts to 3.3%, it is increased by ten times with 31.6% in the case of 13 or more points. A study by Shapiro et al evaluated mortality in patients with suspected infection in the emergency department and found the following in-hospital mortality rates:

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

Apart from lethality predictors 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 an early disturbed tissue oxygenation.

The lethality of sepsis amounts generally to be about 28%. It especially depends on the patient’s age and amounts to about 10% in the case of children, while it is 38% in the case of people above the age of 85.

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 patient at the age of 66 received a total replacement of the left hip due to a 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 deciding for a successful therapy of the 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 which accompany an elevated lethality during the sepsis?

A. Age > 65 years  
B. Thrombocytes < 150.000/mm³  
C. Home residents  
D. Age < 5 years  
E. Respiratory insufficiency

References

J. Schulte am Esch u.a.: MLP Duale Reihe - Anästhesie, Georg Thieme Verlag, 2007


K. Reinhard: S2-Leitlinie Diagnose und Therapie der Sepsis, Thieme, 2007


AWMF-Leitlinie Sepsis

Correct answers: 1E, 2C, 3D

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