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Management of Sepsis in Neutropenic Patients

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

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Publisher

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www.onkopedia-guidelines.info

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Date of document: January 2012

Compliance rules:

- Guideline
- Conflict of interests

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on behalf of the AGIHO Infectious Diseases Working Party of the DGHO

1 Basic Information

Sepsis is a frequent syndrome caused by serious infections in neutropenic patients and remains a leading cause of non-relapse mortality. Clinical symptoms are highly acute. Early treatment with causal and supporting measures may reduce mortality. This guideline on diagnostics and therapy of sepsis was developed by the AGIHO Infectious Diseases Working Party of the DGHO. The majority of recommendations is based on studies in non-neutropenic patients, validated on experience in the care of patients in hematology and oncology.

Categories are based on the evaluation of study results and the recommendations developed by the Infectious Diseases Society of America, ISDA, see Table 1.

Table 1: Categories of Evidence

Category, grade Strength of Recommendation	Definition
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of Evidence	**Definition**
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferable from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports from expert committees

2 Definitions

2.1 Sepsis

Definition is based on the consensus criteria of the Society of Critical Care Medicine (SCC), European Society of Intensive Care Medicine (ESICM), American College of Chest Physicians

(ACCP), American Thoracis Society (ATS) and the Surgical Infection Society (SIS) [1, 2], see Table 2.

Table 2: Diagnostic Criteria of Sepsis

Category	Parameter
General	• Fever (core temperature > 38,3° C) • Hypothermia (core temperature < 36° C) • Heart Rate > 90 b.p.m. or 2SD above the normal value for age • Tachypnea > 30 breaths p.m • Altered mental status • Significant edema or positive fluid balance > 20 ml / kg over 24 h) • Hyperglycemia (plasma glucose > 110 mg / dl or 7,7 mM / l) in the absence of diabetes
Inflammatory	• C reactive protein > 2 SD above the normal value • Procalcitonin > 2 SD above the normal value
Hemodynamic	• Arterial hypotension (systolic blood pressure < 90 mmHg, mean arterial pressure < 70 or a systolic blood pressure decrease > 40 mmHg in adults) • Mixed venous oxygen saturation > 70% • Cardiac Index > 3,5 l / min / m^2
Organ dysfunction parameters	• Arterial hypoxemia (PaO_2/FIO_2 < 300) • Acute oliguria (urine output <0,5 ml / kg / h for at least 2 h) • Creatinine increase ≥ 0,5 mg / dl • Coagulation abnormalities (INR > 1,5 or aPTT > 60 s) • Ileus (absent bowel sounds) • Hyperbilirubinemia (plasma total bilirubin > 4 mg / dl or 70 mmol / l)
Tissue perfusion	• Hyperlactatemia (>3 mmol / l) • Decreased capillary refill or mottling

2.2 Severe Sepsis and Septic Shock

Criteria of severe sepsis and septic shock are summarized in Table 3. [1, 2].

Table 3: Diagnostic Criteria of Severe Sepsis and Septic Shock

Severe Sepsis	Sepsis with new signs of organ dysfunction or a decrease in organ perfusion [lactate acidosis, oliguria (<30 ml/h or <0.5 ml/kg/h), hypotension (<90 mmHg or decrease of >40mm Hg) and mental alteration]
Septic Shock	Severe sepsis and hypotension persistent despite adequate fluid substitution and exclusion for other reasons for hypotension

3 Therapy

Recommendations for treatment of sepsis are summarized for cardiovascular insufficiency in Table 4, for respiratory failure in Table 5, for renal failure in Table 6, nutrition and control of metabolic functions in Table 7, for coagulation disorders in Table 8, for hematopoetic growth factors and immunoglobulins in Table 9, for transfusion in Table 10.

Table 4: Therapy of Sepsis – Cardiovascular Insufficiency

Recommendations	Category of Evidence
Volume substitution can be carried out with crystalloid fluids or colloids.	**A-I**
Human albumin should not be used for volume substitution.	**D-II**
The drug of choice to elevate the vasotonus is norepinephrine.	**B-II**
In case of sepsis-related myocardial depression leading to low cardiac output despite adequate volume substitution, treatment with dobutamine should be instituted.	**A-II**

Table 5: Therapy of Sepsis – Respiratory Failure

Recommendations	Category of Evidence
Noninvasive positive pressure ventilation (CPAP or bilevel positive airway pressure) should be preferred if possible in patients without hypotension or altered mental status.	**A-II**
An early start of noninvasive ventilation, before development of severe hypoxemia, is favorable.	**B-III**

Table 6: Therapy of Sepsis – Renal Dysfunction

Recommendations	Category of Evidence
Intermittent hemodialysis and continuous renal replacement therapies are equivalent.	**B-I**
No firm recommendations can be given for the use of increased doses of renal replacement therapy.	**C-I**
Low-dose dopamine for protection of renal function is not recommended.	**E-I**

Table 7: Therapy of Sepsis – Nutrition and Control of Metabolic Functions

Recommendations	Category of Evidence
Oral diet is preferred over parenteral nutrition.	**A-III**
During initial phase of sepsis, energy supply should not exceed 20–25 kcal/kg IBW.	**D-III**
During recovery, 25–30 kcal/kg IBW should be provided.	**B-III**
Patients with an APACHE II score of 10–15 might benefit from receiving a formulation enriched with arginine, nucleotides and ώ -3-fatty acids.	**B-I**
Mortality of patients with an APACHE II score of >25 might be increased when receiving a formulation enriched with arginine, nucleotides and ώ -3-fatty acids.	**E-II**
Aiming at strictly normal blood glucose level of 4.4–6.6 mmol/l (80–120 mg/dl) is not recommended.	**E-I**
Blood glucose levels should be kept ≤ 8.3 mmol/l (150 mg/dl) in septic neutropenic patients.	**B-III**
Further clinical trials are needed before treatment with selenium can be recommended.	**C-I**
High-dose corticosteroids should not be used in neutropenic or nonneutropenic septic patients.	**E-I**
The use of substitutive doses of hydrocortisone in neutropenic patients with sepsis is not recommended.	**D-I**

Table 8: Therapy of Sepsis – Coagulation

Recommendations	Category of Evidence
Further trials on the use of low-dose heparin (500 IU/h for 7 days) are needed before recommendations can be made.	**C-I**
No evidence-based recommendations on the use of ATIII in neutropenic patients with sepsis can be made.	**C-I**
If contraindications are thoroughly ruled out, the use of APC is recommended in patients with an APACHE II score >25 or a minimum of two organs failing.	**A-I**
The use of APC is not recommended in patients with an APACHE II score <25.	**E-I**

Table 9: Therapy of Sepsis – Hematopoetic Growth Factors and Immunoglobulins

Recommendations	Category of Evidence
The routine additional use of G-CSF or GM-CSF to standard treatment of sepsis in neutropenia is not recommended.	**D-I**
There is moderate degree of evidence to support the use of i.v. immunoglobulins in sepsis.	**B-II**

Table 10: Therapy of Sepsis – Transfusion

Recommendations	Category of Evidence
The cut-off for substitution of platelets is often set to a higher value (platelets 20 000/ll instead of 10,000/ll) during sepsis.	**B-III**
Although there are no prospective randomized studies showing a clinical benefit, hemoglobin levels should be kept >9 g/dl to optimize tissue oxygenation.	**B-III**

9 References

1. Olaf Penack, Dieter Buchheidt, Maximilian Christopeit, Marie von Lilienfeld-Toal, Gero Massenkeil, Marcus Hentrich, Hans Salwender, Hans-Heinrich Wolf, Helmut Ostermann: Management of sepsis in neutropenic patients: Guidelines from the infectious diseases working party of the German Society of Haematology and Oncology. Ann Oncol 22:1019-1029, 2011. DOI:10.1093/annonc/mdq442
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15 Links

https://www.agiho.de/ueber-die-agiho

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17 Disclosures

according to the rules of the responsible Medical Societies.

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according to the rules of the German Association of Hematology and Oncology (*DGHO, Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie*) and the recommendations of the AWMF (version dated April 23, 2010) and international recommendations.