

Xaver Schiel · Holger Hebart · Winfried V. Kern ·  
Michael G. Kiehl · Jens Peter Sölch · Stefan Wilhelm ·  
Helmut Ostermann

## Sepsis in neutropenia

### Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO)

Published online: 9 September 2003  
© Springer-Verlag 2003

**Abstract** Patients developing fever in neutropenia are at high risk of infection-related complications. Their outcome is influenced by the degree of severity (sepsis, severe sepsis and septic shock). Sepsis describes clinical syndromes resulting from systemic inflammatory response. Diagnosis of sepsis is based on simple clinical criteria. Treatment of neutropenic patients with sepsis does not differ from sepsis treatment in non-neutropenic patients. A variety of treatment options have failed (e.g. anti-cytokine strategies, anti-endotoxin antibodies), however, in recent years successful targeted treatment, the use of activated protein C or the substitution of hydrocortisol has been shown to reduce mortality rates. The outcome of neutropenic sepsis is influenced by the underlying disease as well, however survival rates of neutropenic patients

treated on the intensive care unit have improved during the past decade. This paper focuses on pathophysiology, diagnosis and treatment of sepsis. Evidence based medicine (EBM) criteria are used to grade treatment recommendations [50].

**Keywords** Sepsis · Neutropenia · Guideline · Treatment

---

#### Pathophysiology of sepsis

Sepsis describes clinical syndromes resulting from systemic inflammatory response (SIRS). The pathogenetic principle is based upon an amplified inflammatory reaction which is initiated but not necessarily maintained by an infection and which may finally become dysregulated. The key event is a rapid activation of humoral cascade systems (complement, coagulation, kallikrein-kinin system) and of cells that support the inflammatory reaction (granulocytes, monocytes, lymphocytes, macrophages, endothelial cells). These cells, once activated, produce and release inflammatory mediators as well as vasoactive or cytotoxic molecules. This process is characterized by synergistic, antagonistic and numerous redundant interactions. A strict differentiation between mediators and effectors is impossible due to the pleiotropic functions of many of these substances. Of central importance is the immunological reaction to microbial toxins.

Classical pathogens inducing severe sepsis are gram-negative bacteria and their endotoxins (lipopolysaccharide/LPS). Furthermore it has been demonstrated that cell wall components of grampositive bacteria (peptidoglycans, teichoic acid) or fungi as well as exotoxins (toxic shock syndrome toxin-1/TSST-1) can activate these inflammatory cascades. Those molecules bind to membrane-bound and soluble receptors (CD14, mannose binding protein, toll-like receptors/TLR) inducing excessive production and release of pro-inflammatory media-

---

X. Schiel · H. Ostermann (✉)  
Department of Internal Medicine III,  
University of Munich, Hospital Grosshadern,  
Marchioninistrasse 15, 81377 München, Germany  
e-mail: helmut.ostermann@med3.med.uni-muenchen.de

H. Hebart  
Department of Internal Medicine II,  
University of Tuebingen,  
Tuebingen, Germany

W. V. Kern  
Department of Infectious Diseases,  
University of Freiburg,  
Freiburg, Germany

M. G. Kiehl  
Department of Hematology/Oncology,  
Bone Marrow Transplant Unit,  
Idar-Oberstein, Germany

J. P. Sölch  
Amgen GmbH,  
Munich, Germany

S. Wilhelm  
Department of Internal Medicine,  
University of Rostock,  
Rostock, Germany

tors such as tumor-necrosis factor (TNF)-alpha, Interleukin-1 (IL-1) and others [46, 18, 45].

Exotoxins may also act as superantigens. They stimulate T-cells by cross-linking major histocompatibility complex (MHC)—class II with T-cell receptors independent from MHC restriction and antigen specificity [5].

The early phase of sepsis is characterized by an excessive hyperinflammatory reaction of the immune system finally leading to multi-organ failure. The release of anti-inflammatory effectors (IL-4, IL-10, cortisol, etc.) may induce a compensatory anti-inflammatory response syndrome (CARS). Due to this compensatory reaction immunosuppression or anergy may occur. Additional immunosuppression is propagated by apoptotic loss of lymphocytes and dendritic cells, a change in T-cell function and a functional inhibition of macrophages [63]. Secondary infections may lead to repetitive cycles of SIRS and CARS. If signs of SIRS and CARS prevail, a mixed antagonistic response syndrome (MARS) is present [89].

Polymorphisms of genes encoding inflammatory mediators and their promoters influence the physiological activity and expression of specific gene products during the course of the inflammatory reaction. It has been shown that TLR-4 mutations increase the susceptibility for gram-negative infections. Polymorphisms of the TNF-promotor lead to increased TNF levels during sepsis and are associated with poor survival. Further genetic polymorphisms have been described in a number of genes which may influence the clinical course of sepsis [55, 35, 18, 54, 80, 85].

### Organ dysfunction

Organ dysfunction results from direct cytotoxic effects of inflammatory mediators and microbial toxins as well as from dysregulation of micro- and macrocirculation,

oxygen transport and tissue oxygenation. A key role in the pathogenesis of organ dysfunction is thought to be endothelial activation and damage to the microcirculation due to inflammatory infiltration and increased permeability of the vessel wall. Interstitial edema, capillary microembolisation or microthrombi and loss of regulation of the microvascular blood flow lead to perfusion mismatch with a decrease in peripheral vascular resistance.

The decrease in vascular resistance is partially compensated by an increase in heart rate and cardiac output. Potentially reversible myocardial depression often prevents an adequate increase of cardiac output and is thought to be caused by myocardial depressant factors such as toxins, cytokines, metabolic defects of myocytes and downregulation of beta-receptors (septic cardiomyopathy). Additional factors are a decrease in preload induced by a change in ventricular compliance and a decrease in right ventricular venous return (venous pooling, volume deficiency by fluid sequestration).

An important pathophysiological factor is a decrease in tissue oxygenation. Besides a restriction of global oxygen transport (respiratory failure, decrease in cardiac output, anemia), inadequate regional oxygen supply due to perfusion mismatch is of importance. The relevance of disturbances in peripheral oxygen extraction and cellular oxygen metabolism is still undetermined [68].

### Definition

The definition of sepsis suggested by the consensus conference of the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) in 1994, (Table 1), is still regarded as an international standard [52]. Sepsis is defined as a systemic inflammatory reaction induced by microorganisms invading the blood stream and/or their toxins released from a focus of

**Table 1** Definition of sepsis [52]

Infection:	Inflammatory reaction due to the presence of microorganisms or the invasion of otherwise sterile tissue by microorganisms.
Systemic Inflammatory Response Syndrome (SIRS):	Systemic Inflammation as reaction to multiple disease states. The systemic reaction is defined by two or more of the following: <ul style="list-style-type: none"> <li>· Temperature &gt;38°C or &lt;36°C</li> <li>· Heart rate &gt;90/min</li> <li>· Respiration rate &gt;20/min or PaCO<sub>2</sub> &lt;32 mmHg</li> <li>· Leukocytes &gt;12000/μl or &lt;4000/μl or shift to the left &gt;10%</li> </ul>
Sepsis (SIRS + infection):	Systemic reaction to infection. The systemic reaction is defined by two or more of the following: <ul style="list-style-type: none"> <li>· Temperature &gt;38°C or &lt;36°C</li> <li>· Heart rate &gt;90/min</li> <li>· Respiration rate &gt;20/min or PaCO<sub>2</sub> &lt;32 mmHg</li> <li>· Leukocytes &gt;12000/μl or &lt;4000/μl or shift to the left &gt;10%</li> </ul>
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 mm Hg or decrease of >40 mm Hg), mental alteration
Septic Shock:	Severe sepsis and hypotension persistent despite adequate fluid substitution and exclusion for other reasons for hypotension.
Multiple organ dysfunction syndrome (MODS):	Change in organ function in a critically ill patient, restoration of homeostasis requires intervention

infection. This broad definition of sepsis has to be supplemented by criteria related to prognosis and treatment. Among these, the presence and degree of multiple organ dysfunction, and development of septic shock defined by volume-refractory hypotension are important. Septic shock is associated with a worse prognosis than sepsis [70, 72].

The criteria of leukocytosis, leukocytopenia or shift to the left in the differential white blood count can not be used in patients with sepsis in neutropenia. If signs of a systemic inflammatory reaction without an obvious cause other than infection occur in a neutropenic patient, the diagnosis of sepsis in neutropenia has to be made. However, it is important to rule out anemia as a cause for an increase in heart rate.

Although a prospective validation of the consensus criteria for leukocytopenic/neutropenic patients is not available, their use in leukocytopenic patients is recommended, because no criteria for this patient group have been specified as yet.

It could be shown that the prognosis of patients treated on the ICU is determined by the physiological changes induced by the underlying infection, reflected by scoring systems such as APACHE II and SAPS II. However, long-term prognosis of these patients depends upon their malignant disease. This underlines the usefulness of the SAPS II score in leukocytopenic/neutropenic patients (C2) [77].

---

## Incidence of sepsis

Prospective studies using the ACCP/SCCM consensus definition in neutropenic patients are not available. However, it can be assumed that more than 90% of febrile neutropenic episodes fulfill the criteria of sepsis according to the consensus definition. The incidence of these febrile episodes can be calculated by using data from published studies on antimicrobial prophylaxis. The endpoint in these studies was occurrence of fever presumably related to infection. According to these studies, the incidence of sepsis in neutropenia secondary to intensive myelosuppressive chemotherapy is around 70–100% [1, 75, 23, 58]. It has to be considered that the incidence of sepsis is related to the intensity of chemotherapy and the degree and duration of neutropenia as well as the overall performance status and pretreatment of the patient. In allogeneic bone marrow transplant recipients, the incidence of febrile episodes is almost 100%.

In the majority of studies, the incidence of bacteremic infections in neutropenia has been reported to be 10–30% [75, 90, 26]. The incidence of septic shock and severe sepsis has not been reported from the majority of trials. In some studies about 40% of the patients treated by intensive chemotherapy developed severe sepsis or septic shock. As in the non-neutropenic patient population in general, an increase in number and severity of septic episodes can be assumed [58].

---

## Prognostic factors in leukocytopenic patients with sepsis

### Disease associated risk factors

The high incidence of invasive infections in patients with malignancies is mainly due to disease-associated defects of humoral (e.g. in patients with chronic lymphocytic leukemia or multiple myeloma) or cellular defence mechanisms (e.g. in Hodgkin's disease). Main risk factors following cytotoxic chemotherapy are the severity and duration of granulocytopenia [13, 26]. In addition, skin and mucosal barriers can be disrupted by chemotherapy, insertion of catheters (staphylococci, fungi), invasive diagnostic procedures, or by invasive tumor growth (colon cancer) [90]. Decreased production of saliva or retention of secretion due to tumor obstruction (particularly in patients with lung cancer) facilitate the growth of pathogenic microorganisms. Furthermore the incidence of infection is increased in malnourished tumor patients. In immunosuppressed patients, parenteral nutrition increases the risk for infections as well. Hospitalisation and antibiotic pretreatment predispose to nosocomial infections.

### Cytokines

Increased levels of pro-inflammatory (TNF-alpha, IL-6, IL-8) as well as anti-inflammatory cytokines (IL-10, IL-1RA) are found in neutropenic and non-neutropenic patients with sepsis [66, 65, 29].

Severity of sepsis as well as mortality rates are related to cytokine levels. However, these parameters are not used in clinical routine, before technical difficulties have been resolved and therapeutic consequences have been defined.

### Coagulation and fibrinolytic system

Septic shock and multiple organ failure syndrome are often associated with systemic activation of coagulation and fibrinolysis, disseminated fibrin deposition and consumption of coagulation and fibrinolysis inhibitors. Disturbances of hemostasis are of prognostic relevance in sepsis [39, 34, 53, 69, 39]. However, most studies demonstrating these results have been done in non-neutropenic patients with sepsis. For antithrombin and PAI-1, prognostic relevance in neutropenic sepsis could be shown [61, 60].

---

## Treatment

Antimicrobial treatment must be started immediately in order to improve tissue oxygenation, restore cardiovascular function and improve other organ functions. Treatment of sepsis in neutropenic patients should essentially

**Table 2** Pharmacological profiles of inotropic drugs

Substance	Heart rate $\beta_1$	Inotropic $\beta_1$	Vasokonstriction $\alpha_1$	Vasodilatation $\beta_2$	Dopaminergic
Dopamine					
<10 $\mu\text{g}/\text{kg}/\text{min}$	++	++	0	++	++++
>10 $\mu\text{g}/\text{kg}/\text{min}$	++	++	++	0	0
Dobutamine	+	++++	+	++	0
Norepinephrine	++	++	++++	0	0
Epinephrine	++++	++++	++++	+++	0

be the same as in non-neutropenic patients, as specific data for the treatment of sepsis in neutropenic patients are not available. The decision to initiate intensive care treatment has to take into account the prognosis of the underlying disease. If intensive care treatment is necessary in hematological patients mortality is about 50%, whereas in the other half of the patients the sepsis-related organ failure can be managed successfully. Therefore intensive care treatment has to be seen as a therapeutic option in patients with hematological malignancies [11].

#### Antimicrobial treatment

Antimicrobial treatment in neutropenic patients should be empirical in patients without detectable organism or focus of infection. Immediate start of treatment with broad-spectrum antibiotics and the early addition of antifungals in non-responding patients is necessary (see this issue Link et al; Böhme et al).

#### Treatment of Cardiovascular Insufficiency

Aggressive goal-directed treatment aiming at restoration of cardiovascular function has the potential to increase survival of patients with sepsis [71]. Sepsis-induced hypotension is primarily treated by volume substitution [14]. To restore adequate cardiac filling pressures (Goal: central venous pressure 8–12 mm Hg, pulmonary wedge pressure 12–15 mm Hg), crystalloid fluids or colloids can be useful (**A1**) [7, 71, 17, 73] Human albumin however should be used with caution, because in a meta-analysis of 30 studies the application of human albumin was associated with increased mortality [2] (**D2**). Treatment with volume substitution should be done under hemodynamic monitoring (central venous pressure, blood pressure, heart rate, cardiac output, pulmonary wedge pressure and lactate levels). If renal function is impaired, the possibility to eliminate fluids by continuous hemofiltration should be considered, whereas colloids should not be used. Infusion of hydroxyethylstarch (HAES) increases the rate of acute renal failure [76] (**A1**).

If a sufficient mean arterial pressure (>65 mmHg) can not be achieved by volume substitution in a reasonable time frame, treatment with vasopressors is indicated. The drug of choice is norepinephrine in a dose of 0.1–1.3  $\mu\text{g}/\text{kg}/\text{min}$  [56, 57, 59, 86] (**B2**). It could be shown that renal

function is improved by treatment with norepinephrine [36, 24]. The potentially adverse vasopressor actions of norepinephrine as indicated by peripheral vasoconstriction and hypoperfusion in the splanchnic region are diminished in sepsis caused by decreased response of adrenoceptors and sepsis-induced direct vasodilatation. Due to the potentially adverse effects of dopamine and epinephrine, norepinephrine is the drug of choice to elevate vasotonus [56, 78]. Another vasopressor which has been investigated in smaller studies is vasopressin. Vasopressin (0.01–0.04 U/min) did increase urinary output and creatinine clearance in comparison to norepinephrine. The American Heart Association therefore recommends supports its use in refractory septic shock (**B2**) [3]. If sepsis-related myocardial depression leads to low cardiac output despite adequate volume substitution, vasopressor treatment plus dobutamine should be used in order to increase contractility [87, 86] (**A2**). The recommended dose of dobutamine is 2.5–12  $\mu\text{g}/\text{kg}/\text{min}$ . Dobutamine treatment should result in an increase of central venous oxygen saturation to more than 70%, normal lactate level and cardiac index [86].

Epinephrine is used only in combinations to treat cardiovascular insufficiency due to a decrease in intestinal perfusion and because of its arrhythmogenic potential. See Table 2.

The effects of phosphodiesterase inhibitors and dopexamin in the treatment of sepsis have not been well studied. The use of low dose dopamine is not recommended [9] (**D1**).

#### Treatment of pulmonary failure

Besides the restoration of cardiovascular function, hypoxemia caused by pulmonary failure must be prevented to optimise tissue oxygenation. In the awake, cooperative patient with a minor disturbance ( $\text{PaO}_2/\text{FiO}_2 > 200$ ) of gas exchange, an augmentation of spontaneous breathing with intermittent continuous positive airway pressure (CPAP) can be attempted. In moderate to severe respiratory insufficiency, endotracheal intubation and controlled mechanical ventilation are necessary. However, non-invasive positive pressure ventilation (CPAP or bilevel positive airway pressure) has to be considered [42, 41, 20]. For both treatment options it has been shown in selected neutropenic and cancer patients that the necessity of intubation can be significantly reduced in comparison

to control patients [43] (**A2**). A clear-cut recommendation as to when to initiate these measures is not supported by data at this time. Generally an early start is favorable (**B3**). It has to be stated that the use of these measures is depending upon the availability of intensive care facilities, as non-response and necessity for intubation have to be realized promptly. For controlled mechanical ventilation, guidelines established for intensive care medicine should be used [8].

### Renal replacement therapy

Acute renal failure is defined as rapid deterioration of renal function. Clinically, three groups can be distinguished: pre-renal, renal and post-renal failure. In patient with sepsis, pre-renal and renal failure are predominant. Multiple underlying factors such as hemodynamic alterations, damage from microbial toxins, cytokines and drugs are responsible [82]. Renal failure without primary vascular glomerular or interstitial cause is regarded as acute tubular necrosis. Specific treatment for acute tubular necrosis has not yet been specified [51].

Acute renal failure in patients with sepsis necessitates the immediate and early replacement of renal function in order to balance fluids, remove uremic toxins and control electrolytes. Continuous hemofiltration procedures are preferred to intermittent dialysis because they allow controlling fluid balance and eliminating uremic toxins without compromising circulation [10] (**C2**). CVVH (continuous veno-venous hemofiltration) should be used in patients with instable cardiovascular function as compared to CAVH (continuous arterio-venous hemofiltration). These suggestions are however based on studies with small numbers of patients. A meta-analysis of 13 studies with 1400 patients could not demonstrate any advantage of CVVH compare to intermittent dialysis [49].

Prolonged use of low dose dopamine for protection of renal function is not useful [9] (**D1**).

Large prospective clinical studies on the usefulness of elimination of toxins and mediators of inflammation by extracorporeal measures such as hemofiltration, plasmapheresis, and hemoperfusion have not shown a significant benefit [81, 19] (**C2**).

### Nutrition and control of metabolic functions

In critically ill patients, catabolic and anabolic phases are observed [79]. The first days are characterized by extended catabolism resulting in a negative nitric balance. To keep catabolism in septic patients as low as possible, it is recommended to increase caloric intake by 30–50% above the usual amount of 30–35 kcal/kg/day. Enteral nutrition should be preferred to parenteral nutrition (PN) to maintain the integrity of the mucosal barrier [47]. A normal intestinal mucosal barrier prevents the translocation of microbial organisms and their toxins. However, in many cases it is difficult to assess the performance of the

gastrointestinal tract, therefore PN may be necessary. PN should be composed of glucose (3–4 g/kg/day), amino acids (1.5–2.0 g/kg/day) and lipids (0.5–1.5 g/kg/day, 20% emulsion as continuous infusion). The calculation should be based on idealized body weight. Substitution or restriction of electrolytes has to be adapted to the clinical situation (e.g. diarrhea, renal failure). In patients undergoing long-term PN, vitamins and trace elements have to be supplemented.

Despite the association of hypoalbuminemia and severe malnutrition, a positive impact of albumin substitution on morbidity or mortality in sepsis patients has not been found. A so-called immunonutrition (e.g. high dose arginine, glutamine, omega-3-fatty acids or nucleotides) can not be generally recommended [40,16] (**C3**).

### Corticosteroids

Due to their anti-inflammatory properties, the usefulness of corticosteroids for the treatment of sepsis has repeatedly been investigated. A meta-analysis of studies published between 1963 and 1988 could not demonstrate a benefit from the use of steroids in patients with sepsis severe sepsis and septic shock [22]. Thus, the use of corticosteroids in high doses in severe sepsis and septic shock is not recommended (**D2**).

In many patients with sepsis, a relative adrenal insufficiency can be observed. Recent studies in non-neutropenic patients with sepsis could show a reduction of mortality in patients treated with substitutive doses of hydrocortisol [6,15,21] (**A1**).

### Treatment with coagulation inhibitors

Septic shock is often associated with disseminated activation of coagulation leading to fibrin deposition in the microcirculation. Multiple organ dysfunction syndrome is probably correlated to disseminated coagulation activation. Early studies used heparin to prevent coagulation activation. However, these studies have not shown a significant benefit with regards to the occurrence of MODS or mortality [30]. Thus heparin should only be used in sepsis and disseminated intravascular coagulation (DIC) if a patient has additional complications such as venous or arterial thromboembolism. In patients with hematological malignancies, the increased risk of bleeding associated with the use of heparin has to be considered, as many of these patients have a treatment-related thrombocytopenia.

The rationale for the use of antithrombin in sepsis is based upon observations that endotoxin or gramnegative bacteria induce DIC in animal studies. This can be prevented and mortality can be significantly reduced by the application of antithrombin [83, 27, 38, 28, 62]. Furthermore low antithrombin levels are of high prognostic value concerning mortality of septic shock in non-neutropenic as well as in neutropenic sepsis [34,61]. In a

randomized, double-blind, placebo-controlled study in patient with septic shock and DIC, the use of antithrombin led to a reduction in the duration of DIC. Therefore, antithrombin is recommended for the treatment for DIC (**A1**). Sepsis however is not a valid indication for antithrombin, as in a large randomized, placebo-controlled study, no reduction of mortality by antithrombin could be shown [88] (**D1**). However, the group of patients who did not receive concomitant heparin with antithrombin treatment did have a survival benefit. These results support the notion of a negative influence of heparin on antithrombin by preventing the cellular effects of antithrombin due to binding to circulating heparin. Experimental data support this hypothesis by showing that heparin together with antithrombin leads to an impairment of microcirculation [44].

Activated protein C inhibits coagulation factors Va and VIIIa. Furthermore, it has anti-inflammatory properties by reducing the activity of NF $\kappa$ B and therefore cytokine expression in monocytes. Activated protein C has been shown to reduce 28-day sepsis mortality by 6% [12] (**A1**). However, patients with neutropenia or thrombocytopenia were excluded from this study. It is therefore uncertain if these results can be applied to neutropenic patients as well.

#### Anti-cytokine treatment and hematopoietic growth factors

The central role of cytokines during the hyper- and anti-inflammatory phases of sepsis induced clinical studies on the use of cytokines and cytokine inhibitors as therapeutic agents. However, results of clinical trials did not show any survival benefit. In an open, placebo-controlled phase II trial, recombinant IL-1 receptor antagonist led to a dose-dependent reduction of mortality in patients with sepsis or septic shock [33]. However, this could not be confirmed in two double-blind, randomized, placebo-controlled phase III trials [64, 32] (**E1**).

In clinical studies, TNF inhibitors did not improve the survival of patients with sepsis as well [37, 91]. For a TNF-receptor:Fc fusion protein, increased mortality of patients with septic shock was reported [31] (**E1**). Recent observations of sepsis and other infectious events in patients with rheumatoid arthritis treated with TNF inhibitors strongly suggest that TNF plays an essential role in the immune response to infection [48].

Some patients with neutropenic fever are at higher risk for infection-related complications. The use of colony stimulating factors (G-CSF or GM-CSF) can be considered in these patients, but the benefits in that setting have not been proven. Risk factors include neutrophil counts below 100/ $\mu$ l, MODS, pneumonia, invasive fungal infection or septic shock [67] (**B2**).

First results of studies on the use of interferon-(gamma) showed improvement of survival in a subset of patients with sepsis [25]. These data may corroborate the concept of an effective immune-stimulating therapy, which restores the function of immune cells such as

macrophages (HLA-DR expression, TNF expression) in patients with sepsis.

#### Immunoglobulins

The rationale for the use of polyvalent immunoglobulin in sepsis is based upon the model of an elimination of microbes or their toxins by increasing opsonization and interaction with cytokines. A Cochrane analysis of 492 patients from 11 studies who received additional treatment with polyvalent immunoglobulin in septic shock or severe sepsis could show an advantage for the immunoglobulin treatment. Relative risk was 0.64 (95% CI 0.51–0.80) favoring the immunoglobulin-treated group [4]. However in this analysis, studies with newborns were included as well. If only adult patients were analyzed, only 251 patients from 6 studies could be evaluated. The relative risk remained unchanged. Since only two of these studies were double-blind and randomized, and the result of this meta-analysis is based upon a small data pool, the general treatment recommendation has to be seen critical (**C2**).

A recently published prospective randomized controlled trial in 42 patients with severe sepsis using an IgM enriched preparation could not show any benefit [84] (**D2**).

#### Transfusion management in sepsis

The recommendations for substituting platelets or packed red blood cell in neutropenic patients can be applied to those patients developing sepsis as well. However the cutoff for substitution is often set to a higher value (platelets 20.000/ $\mu$ l instead of 10.000/ $\mu$ l) [74]. To optimize tissue oxygenation, hemoglobin levels should be kept above 9 g/dl (**C3**).

#### References

1. (1984) Trimethoprim-sulfamethoxazole in the prevention of infection in neutropenic patients. EORTC International Antimicrobial Therapy Project Group. *J Infect Dis* 150:372–379
2. (1998) Human albumin administration in critically ill patients: systematic review of randomised controlled trials. Cochrane Injuries Group Albumin Reviewers. *BMJ* 317:235–240
3. (2000) Part 6: advanced cardiovascular life support. Section 6: pharmacology II: agents to optimize cardiac output and blood pressure. European Resuscitation Council. *Resuscitation* 46:155–162
4. Alejandria MM, Lansang MA, Dans LF, Mantaring JB (2002) Intravenous immunoglobulin for treating sepsis and septic shock. *Cochrane Database Syst Rev* CD001090
5. Alouf JE, Muller-Alouf H (2003) Staphylococcal and streptococcal superantigens: molecular, biological and clinical aspects. *Int J Med Microbiol* 292:429–440
6. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, Chaumet-Riffaut P, Bellissant E (2002) Effect of treatment with

- low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 288:862–871
7. Astiz ME, Rackow EC (1999) Crystalloid-colloid controversy revisited. *Crit Care Med* 27:34–35
  8. Azoulay E, Alberti C, Bornstain C, Leleu G, Moreau D, Recher C, Chevret S, Le G, Brochard L, Schlemmer B (2001) Improved survival in cancer patients requiring mechanical ventilatory support: impact of noninvasive mechanical ventilatory support. *Crit Care Med* 29:519–525
  9. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J (2000) Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet* 356:2139–2143
  10. Bellomo R, Ronco C (2000) Continuous haemofiltration in the intensive care unit. *Crit Care* 4:339–345
  11. Benoit DD, Vandewoude KH, Decruyenaere JM, Hoste EA, Colardyn FA (2003) outcome and early prognostic indicators in patients with a hematologic malignancy admitted to intensive care unit for a life-threatening complication. *Crit Care Med* 31:104–112
  12. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr (2001) Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 344:699–709
  13. Bodey GP, Buckley M, Sathe YS, Freireich EJ (1966) Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 64:328–340
  14. Boldt J, Muller M, Mentges D, Papsdorf M, Hempelmann G (1998) Volume therapy in the critically ill: is there a difference? *Intensive Care Med* 24:28–36
  15. Briegel J, Forst H, Haller M, Schelling G, Kilger E, Kuprat G, Hemmer B, Hummel T, Lenhart A, Heyduck M, Stoll C, Peter K (1999) Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. *Crit Care Med* 27:723–732
  16. Buchman AL (2001) Glutamine: commercially essential or conditionally essential? A critical appraisal of the human data. *Am J Clin Nutr* 74:25–32
  17. Choi PT, Yip G, Quinonez LG, Cook DJ (1999) Crystalloids vs. colloids in fluid resuscitation: a systematic review. *Crit Care Med* 27:200–210
  18. Cohen J (2002) The immunopathogenesis of sepsis. *Nature* 420:885–891
  19. Cole L, Bellomo R, Hart G, Journois D, Davenport P, Tipping P, Ronco C (2002) A phase II randomized, controlled trial of continuous hemofiltration in sepsis. *Crit Care Med* 30:100–106
  20. Conti G, Marino P, Cogliati A, Dell U, Lappa A, Rosa G, Gasparetto A (1998) Noninvasive ventilation for the treatment of acute respiratory failure in patients with hematologic malignancies: a pilot study. *Intensive Care Med* 24:1283–1288
  21. Cooper MS, Stewart PM (2003) Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 348:727–734
  22. Cronin L, Cook DJ, Carlet J, Heyland DK, King D, Lansang MA, Fisher CJ Jr (1995) Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature [see comments]. *Crit Care Med* 23:1430–1439
  23. Cruciani M, Rampazzo R, Malena M, Lazzarini L, Todeschini G, Messori A, Concia E (1996) Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. *Clin Infect Dis* 23:795–805
  24. Desjars P, Pinaud M, Bugnon D, Tasseau F (1989) Norepinephrine therapy has no deleterious renal effects in human septic shock. *Crit Care Med* 17:426–429
  25. Docke WD, Randow F, Syrbe U, Krausch D, Asadullah K, Reinke P, Volk HD, Kox W (1997) Monocyte deactivation in septic patients: restoration by IFN-gamma treatment. *Nat Med* 3:678–681
  26. Elting LS, Rubenstein EB, Rolston KV, Bodey GP (1997) Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. *Clin Infect Dis* 25:247–259
  27. Emerson TE Jr, Fournel MA, Leach WJ, Redens TB (1987) Protection against disseminated intravascular coagulation and death by antithrombin-III in the *Escherichia coli* endotoxemic rat. *Circ Shock* 21:1–13
  28. Emerson TE Jr, Fournel MA, Redens TB, Taylor FB Jr (1989) Efficacy of antithrombin III supplementation in animal models of fulminant *Escherichia coli* endotoxemia or bacteremia. *Am J Med* 87: 27S–33S
  29. Engel A, Kern P, Kern WV (1996) Levels of cytokines and cytokine inhibitors in the neutropenic patient with alpha-hemolytic streptococcus shock syndrome. *Clin Infect Dis* 23:785–789
  30. Feinstein DI (1982) Diagnosis and management of disseminated intravascular coagulation: the role of heparin therapy. *Blood* 60:284–287
  31. Fisher CJ Jr, Agosti JM, Opal SM, Lowry SF, Balk RA, Sadoff JC, Abraham E, Schein RM, Benjamin E (1996) Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. The Soluble TNF Receptor Sepsis Study Group. *N Engl J Med* 334:1697–1702
  32. Fisher CJ Jr, Dhainaut JF, Opal SM, Pribble JP, Balk RA, Slotman GJ, Iberti TJ, Rackow EC, Shapiro MJ, Greenman RL, et al (1994) Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group [see comments]. *JAMA* 271:1836–1843
  33. Fisher CJ Jr, Slotman GJ, Opal SM, Pribble JP, Bone RC, Emmanuel G, Ng D, Bloedow DC, Catalano MA (1994) Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: A randomized, open-label, placebo-controlled multicenter trial. *Crit Care Med* 22:12–21
  34. Fourrier F, Chopin C, Goudemand J, Hendrycx S, Caron C, Rime A, Marey A, Lestavel P (1992) Septic shock, multiple organ failure, and disseminated intravascular coagulation. Compared patterns of antithrombin III, protein C, and protein S deficiencies [see comments]. *Chest* 101:816–823
  35. Freeman BD, Buchman TG (2000) Gene in a haystack: tumor necrosis factor polymorphisms and outcome in sepsis. *Crit Care Med* 28:3090–3091
  36. Fukuoka T, Nishimura M, Imanaka H, Taenaka N, Yoshiya I, Takezawa J (1989) Effects of norepinephrine on renal function in septic patients with normal and elevated serum lactate levels. *Crit Care Med* 17:1104–1107
  37. Grimminger F, Mayer K, Seeger W (1997) Gibt es eine gesicherte Immuntherapie bei der Sepsis? *Internist* 38:541–552
  38. Hauptman JG, Hassouna HI, Bell TG, Penner JA, Emerson TE (1988) Efficacy of antithrombin III in endotoxin-induced disseminated intravascular coagulation. *Circ Shock* 25:111–122
  39. Hesselvik JF, Blomback M, Brodin B, Maller R (1989) Coagulation, fibrinolysis, and kallikrein systems in sepsis: relation to outcome. *Crit Care Med* 17:724–733
  40. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U (2001) Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA* 286:944–953
  41. Hilbert G, Gruson D, Vargas F, Valentino R, Chene G, Boiron JM, Pigneux A, Reiffers J, Gbikpi B, Cardinaud JP (2000) Noninvasive continuous positive airway pressure in neutropenic patients with acute respiratory failure requiring intensive care unit admission. *Crit Care Med* 28:3185–3190
  42. Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi B, Dupon M, Reiffers J, Cardinaud JP (2001) Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med* 344:481–487
  43. Hill NS (2001) Noninvasive ventilation for immunocompromised patients. *N Engl J Med* 344:522–524

44. Hoffmann JN, Vollmar B, Romisch J, Inthorn D, Schildberg FW, Menger MD (2002) Antithrombin effects on endotoxin-induced microcirculatory disorders are mediated mainly by its interaction with microvascular endothelium. *Crit Care Med* 30:218–225
45. Horn DL, Morrison DC, Opal SM, Silverstein R, Visvanathan K, Zabriskie JB (2000) What are the microbial components implicated in the pathogenesis of sepsis? Report on a symposium. *Clin Infect Dis* 31:851–858
46. Hotchkiss RS, Karl IE (2003) The pathophysiology and treatment of sepsis. *N Engl J Med* 348:138–150
47. Kaminski MV Jr, Blumeyer TJ (1993) Metabolic and nutritional support of the intensive care patient. Ascending the learning curve. *Crit Care Clin* 9:363–376
48. Keane J, Gershon S, Wise RP (2001) Tuberculosis associated with infliximab, a tumor necrosis factor (alpha)-neutralizing agent. *N Engl J Med* 345:1098–1104
49. Kellum JA, Angus DC, Johnson JP, Leblanc M, Griffin M, Ramakrishnan N, Linde-Zwirble WT (2002) Continuous versus intermittent renal replacement therapy: a meta-analysis. *Intensive Care Med* 28:29–37
50. Kish MA (2001) Guide to development of practice guidelines. *Clin Infect Dis* 32:851–854
51. Lameire N, Vanholder R (2001) Pathophysiologic features and prevention of human and experimental acute tubular necrosis. *J Am Soc Nephrol* 12 (Suppl 17):S20–S32
52. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 31:1250–1256
53. Lorente F, Landin L, De Pablo R, Renes E, Liste D (1993) L-arginine pathway in the sepsis syndrome [see comments]. *Crit Care Med* 21:1287–1295
54. Lorenz E, Mira JP, Cornish KL, Arbour NC, Schwartz DA (2000) A novel polymorphism in the toll-like receptor 2 gene and its potential association with staphylococcal infection. *Infect Immun* 68:6398–6401
55. Lorenz E, Mira JP, Frees KL, Schwartz DA (2002) Relevance of mutations in the TLR4 receptor in patients with gram-negative septic shock. *Arch Intern Med* 162:1028–1032
56. Martin C, Papazian L, Perrin G, Saux P, Gouin F (1993) Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? *Chest* 103:1826–1831
57. Martin C, Viviani X, Leone M, Thirion X (2000) Effect of norepinephrine on the outcome of septic shock. *Crit Care Med* 28:2758–2765
58. Martin GS, Mannino DM, Eaton S, Moss M (2003) The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 348:1546–1554
59. Meier-Hellmann A (2000) [Catecholamine therapy in sepsis]. *Anaesthesist* 49:1069–1076
60. Mesters RM, Florke N, Ostermann H, Kienast J (1996) Increase of plasminogen activator inhibitor levels predicts outcome of leukocytopenic patients with sepsis. *Thromb Haemost* 75:902–907
61. Mesters RM, Mannucci PM, Coppola R, Keller T, Ostermann H, Kienast J (1996) Factor VIIa and antithrombin III activity during severe sepsis and septic shock in neutropenic patients. *Blood* 88:881–886
62. Minnema MC *CAJP* (2000) Recombinant human antithrombin III improves survival and attenuates inflammatory responses in baboons lethally challenged with *Escherichia coli*. *Blood* 95:1117–1123
63. Oberholzer A, Oberholzer C, Moldawer LL (2001) Sepsis syndromes: understanding the role of innate and acquired immunity. *Shock* 16:83–96
64. Opal SM, Fisher CJ Jr, Dhainaut JF, Vincent JL, Brase R, Lowry SF, Sadoff JC, Slotman GJ, Levy H, Balk RA, Shelly MP, Pribble JP, LaBrecque JF, Lookabaugh J, Donovan H, Dubin H, Baughman R, Norman J, DeMaria E, Matzel K, Abraham E, Seneff M (1997) Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: A phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med* 25:1115–1124
65. Ostermann H, Kratz-Albers K, Mesters RM, Kiehl M, Kienast J (1997) Reciprocal changes in circulating interleukin-6 and its soluble receptor during evolving sepsis in leukocytopenic patients. *J Infect Dis* 176:825–828
66. Ostermann H, Rothenburger M, Mesters RM, van de Loo J, Kienast J (1994) Cytokine response to infection in patients with acute myelogenous leukaemia following intensive chemotherapy. *Br J Haematol* 88:332–337
67. Ozer H, Armitage JO, Bennett CL, Crawford J, Demetri GD, Pizzo PA, Schiffer CA, Smith TJ, Somlo G, Wade JC, Wade JL III, Winn RJ, Wozniak AJ, Somerfield MR (2000) 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. *J Clin Oncol* 18:3558–3585
68. Parillo JE (1993) Pathogenetic mechanisms of septic shock. *N Engl J Med* 328:1471–1477
69. Pralogn G, Calandra T, Glauser MP, Schellekens J, Verhoef J, Bachmann F, Kruihof EK (1989) Plasminogen activator inhibitor 1: a new prognostic marker in septic shock. *Thromb Haemost* 61:459–462
70. Regazzoni CJ, Khoury M, Irrazabal C, Myburg C, Galvalisi NR, O'Flaherty M, Sarquis SG, Poderoso JJ (2003) Neutropenia and the development of the systemic inflammatory response syndrome. *Intensive Care Med* 29:135–138
71. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345:1368–1377
72. Salvo I, de Cian W, Musicco M, Langer M, Piadena R, Wolfler A, Montani C, Magni E (1995) The Italian SEPSIS study: preliminary results on the incidence and evolution of SIRS, sepsis, severe sepsis and septic shock. *Intensive Care Med* 21 (Suppl 2):S244–S249
73. Schierhout G, Roberts I (1998) Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. *BMJ* 316:961–964
74. Schiffer CA, Anderson KC, Bennett CL, Bernstein S, Elting LS, Goldsmith M, Goldstein M, Hume H, McCullough JJ, McIntyre RE, Powell BL, Rainey JM, Rowley SD, Rebullia P, Troner MB, Wagnon AH (2001) Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 19:1519–1538
75. Schonbohn H, Schuler M, Kolbe K, Peschel C, Huber C, Bemb W, Aulitzky WE (1995) Plasma levels of IL-1, TNF alpha, IL-6, IL-8, G-CSF, and IL-1-RA during febrile neutropenia: results of a prospective study in patients undergoing chemotherapy for acute myelogenous leukemia. *Ann Hematol* 71:161–168
76. Schortgen F, Lacherade JC, Bruneel F, Cattaneo I, Hemery F, Lemaire F, Brochard L (2001) Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study. *Lancet* 357:911–916
77. Sculier JP, Paesmans M, Markiewicz E, Berghmans T (2000) Scoring systems in cancer patients admitted for an acute complication in a medical intensive care unit. *Crit Care Med* 28:2786–2792
78. Sharma VK, Dellinger RP (2003) The International Sepsis Forum's controversies in sepsis: my initial vasopressor agent in septic shock is norepinephrine rather than dopamine. *Crit Care* 7:3–5
79. Souba WW (1997) Nutritional support. *N Engl J Med* 336:41–48
80. Stuber F (2001) Effects of genomic polymorphisms on the course of sepsis: is there a concept for gene therapy? *J Am Soc Nephrol* 12 (Suppl 17):S60–S64
81. Surgenor SD, Corwin HL (2000) Hemofiltration in sepsis: is removal of "bad humors" the answer? *Crit Care Med* 28:3751–3752

82. Thijs A, Thijs LG (1998) Pathogenesis of renal failure in sepsis. *Kidney Int* 66 (Suppl):S34–S37
83. Triantaphyllopoulos DC (1984) Effects of human antithrombin III on mortality and blood coagulation induced in rabbits by endotoxin. *Thromb Haemost* 51:232–235
84. Tugrul S, Ozcan PE, Akinci O, Seyhun Y, Cagatay A, Cakar N, Esen F (2002) The effects of IgM-enriched immunoglobulin preparations in patients with severe sepsis [ISRCTN28863830]. *Crit Care* 6:357–362
85. van der Pol WL, Huijzinga TW, Vidarsson G, van der Linden MW, Jansen MD, Keijsers V, de Straat FG, Westerdal NA, de Winkel JG, Westendorp RG (2001) Relevance of Fcγ receptor and interleukin-10 polymorphisms for meningococcal disease. *J Infect Dis* 184:1548–1555
86. Vincent JL (2001) Hemodynamic support in septic shock. *Intensive Care Med* 27 (Suppl 1):S80–S92
87. Vincent JL, Van der LP, Domb M, Bleic S, Azimi G, Bernard A (1987) Dopamine compared with dobutamine in experimental septic shock: relevance to fluid administration. *Anesth Analg* 66:565–571
88. Warren BL EASP (2001) High-dose antithrombin III in severe sepsis a randomized controlled trial. *JAMA* 286:1869–1878
89. Weigand MA, Bardenheuer HJ, Bottiger BW (2003) [Clinical management of patients with sepsis]. *Anaesthesist* 52:3–22
90. Wisplinghoff H, Seifert H, Wenzel RP, Edmond MB (2003) Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. *Clin Infect Dis* 36:1103–1110
91. Zanetti G, Glauser MP (1997) Prevention and treatment of sepsis and septic shock. *Curr Opin Infect Dis* 10:139–143