CONSENSUS STATEMENT ON THE TREATMENT OF SEPTIC SHOCK

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INTRODUCTION

Septic shock represents one of the most difficult management problems for the critical care clinician. The present work is an attempt to give an overview of present day standards of care of septic shock and to formulate recommendations to therapy based on the sound principles of Evidence-Based-Medicine (EBM) (1, 2). We focus on the early (24 to 48 hours) clinical management of septic shock patients and not on the prolonged care of critically ill patients with multi-organ dysfunction.

Application of the principles of EBM in this particular field has some important limitations.

Firstly, large randomized, controlled trials with well predefined end points, which yield the best (level I) evidence, are not always available because of evident difficulties to perform these studies in the setting of septic shock. Secondly, up till 1992, no uniform definition for sepsis and septic shock existed (3). Consequently, conclusions of "older" trials should be very cautiously interpreted and translated to clinical practice. The 1992 definitions are already challenged by opinion leaders (4), and the more recent trials in septic shock patients are frequently criticized because of inadequate selection of cases (lack of definition of infectious focus, different sources of infection, inclusion at different stages of illness, varying underlying health status and age, varying severity of disease, ...), too low numbers of included patients, lack of clinically relevant end points, ... Hence, as could be expected, a surprisingly low number of level I studies were included in an extensive very recent overview of hemodynamic support in sepsis, published on behalf of the American College of Critical Care Medicine (5). We therefore did not attempt to use the EBM 's rating system for the issues we address in this review. We are well aware that the recommendations we formulate will not give the final answers to the multiple questions the clinician is faced with when caring for patients with septic shock.

METHODOLOGY

The purpose of this document is to provide guidelines for physicians to use in septic shock, based on evidence gathered from meta-analyses and consensus conferences from the 1990's supplemented by original articles published in the last two to three years.

At the occasion of its symposium on Evidence-Based Medicine organized in the fall of 1999, The Belgian Society of Internal Medicine decided to invite the board of the Belgian Society of Intensive Care Medicine and Emergency Medicine (SIZ), the Belgian Society for Emergency and Disaster Medicine (Besedim) and the Belgian Society for Infectious Diseases and Clinical Microbiology to co-operate on a consensus statement on the treatment of septic shock. The three invited societies designated each two representatives, working in university hospitals who agreed to answer to a number of key questions formulated by the co-ordinator of the project, being member of the board of the Belgian Society of Internal Medicine.

The members of the panel were asked to base their answers not on their personal expertise but on (recent) evidence, published in top journals and to focus on clinical evidence and relevance and not on experimental data nor on potentially useful novel biological therapeutic interventions undergoing clinical trials. The original

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data which were studied in recent meta-analyses or consensus conferences published in top journals were not checked. However, additional insights resulting from important recent prospective randomised controlled trials on the same topic could modify the recommendation. The participants were asked to use their personal expertise to decide whether the published evidence is applicable to the present day Belgian critical care patient with septic shock. We did not intend to perform cost benefit analyses for this difficult clinical problem.

Due to time constraint, extensive discussions between the three different groups of the panel were not possible. The co-ordinator summarized and streamlined the answers and wrote the final text. During the symposium the audience will be invited to give their comments which may be published in Acta Clinica Belgica as letters to the editor.

1. DEFINITION OF SEPSIS AND SEPTIC SHOCK

A decade ago, no uniform definition of sepsis and septic shock existed. Criteria for diagnosing systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, have been proposed by an expert consensus conference of the American College of Chest Physicians and the Society of Critical Care (3).

Sepsis is defined as an infection-induced SIRS. SIRS is characterized by at least two of the following features 1) fever (> 38° C) or hypothermia (< 36° C) 2) tachycardia (> 90 beats/min.) 3) tachypnea (> 20 respirations/min.) 4) leukocytosis (> 12000 cells/mm^3) or leukopenia (< 4000 cells/mm^3) or the presence of more than 10% immature neutrophils. Sepsis is a SIRS with a definite site of infection.

Severe sepsis is sepsis with at least one failing organ system (kidney, lungs, heart, liver, central nervous system, coagulation, ...), hypoperfusion or hypotension (systolic blood pressure < 90 mm Hg or a reduction of ≥ 40 mm Hg from baseline) that responds to volume therapy alone. A problem here is the lack of criteria to define organ failure and the use of different indices and scoring systems.

Septic shock is severe sepsis requiring the use of inotropic/vasopressor drugs.

Sepsis, severe sepsis and septic shock are different stages of an increasingly severe and overly activated inflammatory response. The definitions were proposed as means to standardize inclusion criteria of patients in clinical trials and have recently been challenged by respected investigators (4).

2. CARDIOVASCULAR SUPPORT

2.1 Fluid therapy

Absolute or relative hypovolemia is invariably present in septic shock. Restoration of volume deficit is essential and is considered as a first line priority to improve survival of patients with sepsis (5-7). Fluid infusion should be titrated to achieve well defined clinical end points such as systolic blood pressure of at least 90 mm Hg or mean arteriel pressure of > 60 mm Hg, heart rate below 120 beats/min, urine output of 0,5 ml/kg/hr and improved mental status and skin perfusion (5). Despite the importance of fluid therapy, controversy still exists over the choice of crystalloids or colloids as the ideal resuscitation fluid, mainly because correctly performed and controlled clinical studies comparing their respective effects are still lacking (7).

Hemodynamic correction is achievable with either type of fluid without pulmonary adverse effects, provided left ventricular filling pressure is maintained below a critical value of 15 mm Hg. The volume of crystalloids necessary to achieve the same end-points is two to four times greater than for colloids (5, 7).

Among crystalloids, normal saline (0.9% NaCl) and Ringer's lactated solution are favoured, while use of glucose 5% solution is discouraged because of the rapid "leakage" from intravascular space. In contrast with traumatic hypovolemic shock, data regarding the use of hypertonic saline solutions in septic shock are lacking.

Several colloid solutions are presently available. Hydroxy-ethyl starch (hetastarch) and gelatin are the most commonly used synthetic colloids in Belgium for fluid resuscitation while the use of plasma protein and albumin solutions declined since 1995.Two recent meta-analyses revealed that the use of colloids, be it albumin or synthetic colloids, as compared with crystalloids increased the risk of death in critical care patients with hypovolemia (8, 9) These meta-analyses, however, grouped very heterogeneous populations (burns, trauma, critical care, cardiac surgery...) treated with different fluid management protocols, drugs and resuscitation monitoring strategies. Hence, the conclusions may not be directly applicable to fluid resuscitation in septic shock. The potentially deleterious effect of colloids could be due to intracellular dehydration and hence cellular "dysfunction", induced by the fluid move from intracellular to extracellular (10). This might be the pathophysiological mechanism explaining the excess mortality in patients treated with colloids since no difference in cardiac failure, a feared complication, was

found in these studies. We probably should not entirely discard albumin solutions. Treatment with albumin infusion (in addition to antibiotic therapy) was recently reported to reduce mortality rate in cirrhotic patients with spontaneous bacterial peritonitis. Shock, however, was an exclusion criterion (11).

Rigorously conducted trials will be needed before a final answer can be given to the question which type of fluid should preferentially be given in septic shock patients. However, the published evidence argues rather against than for colloids, particularly albumin (8, 9). At present, no specific recommendations can be made concerning the choice between different synthetic colloids for resuscitation in septic shock.

2.2 Red blood cell transfusion

Available guidelines for transfusion are based on a consensus of experts, not on data from controlled clinical trials (12). A recent prospective randomized (unblinded, of course) trial evaluating red-cell transfusion practices in 838 intensive care patients revealed a significantly lower overall in-hospital mortality rate in the restrictive-transfusion strategy group (hemoglobin value maintained at a level between 7 and 9 g/dl) as compared to the liberal-strategy group (hemoglobin value maintained at a level between 10 and 12 g/dl) (13). This physiopathologically unexpected result deserves our attention but should take into account that the included patients were euvolemic and that transfusion practices in (septic) shock patients were not addressed. However, similarity is striking with the trials showing that therapy aimed to achieve supranormal oxygen delivery to counteract the "oxygen debt" failed to improve survival and might even be detrimental in critically ill patients (14-16).

A rather restrictive red blood cell transfusion strategy may be adopted in patients with septic shock (5). No evidence based guidelines can be offered, particularly not for subgroups with cardiac or cerebrovascular disease or older patients.

2.3 Vasopressor therapy

A large number of studies on the use of vasopressor and inotropic agents are available but only a few studied important end points such as time to discharge from the ICU, time to reversal of shock and survival. Due to constraints of space, we base our recommendations on these particular issues on the most recent consensus statement, unless stated otherwise (5).

Vasopressor therapy is started preferentially after aggressive fluid resuscitation but occasionally should be initiated immediately. Patients with persistent shock, not responsive to fluid therapy, are treated with vasopressors.

Noradrenaline at doses of 0.2 to 1.5 µg/kg/min and dopamine at doses of 10 to 25µg/kg/min are the agents of choice (5). Noradrenaline has been shown to be more potent than dopamine in reversing hypotension in septic shock (17). Adrenaline should be used as a last resort drug. Phenylephrine is rarely used (5, 18).

2.4 Inotropic therapy

Although most septic shock patients are hyperdynamic, provided adequate fluid therapy is given, cardiac contractility, as assessed by ejection fraction, is impaired. Dobutamine is the inotropic agent of choice, adrenaline is again last resort agent, experience with dopexamine is limited and dopamine seems to exert more inotropic effects than previously thought. Phosphodiesterase inhibitors have not been studied in septic shock patients and have probably no place in view of their vasodilator effects (5).In the 1980's and early 1990's it has been suggested that oxygen delivery (DO_2) should be routinely increased above 600 ml/min/m^2 in septic shock patients by the use of agressive fluid therapy, red blood cell transfusions and inotropic agents. However a meta-analysis and recent studies showed that interventions to maximize DO_2 do not affect mortality rate (14-16).

Therefore, inotropic support should be reserved to patients with absolute or relative cardiac failure. Interventions to routinely achieve supranormal hemodynamic values are no longer recommended (5).

Several studies have investigated the potential benefits from *combining catecholamines* in septic shock. The design of these studies is too poor to yield any evidence that clinical outcome might improve (5)

2.5 Low dose dopamine therapy

Little is known about clinically relevant renal or splanchnic effects of dopamine during septic shock. Juste et al.[19] showed that low dose dopamine in conjunction with high dose noradrenaline significantly increased systolic blood pressure, cardiac output and urine flow (19). There is no evidence for routine administration of low-dose dopamine to protect and/or improve renal function or to enhance splanchnic perfusion in patients with septic shock (5).

3. PULMONARY SUPPORT

Respiratory system dysfunction is invariably present in patients with septic shock. However, one has to differentiate between common functional abnormalities in pulmonary gas exchange and occurrence of the Adult Respiratory Distress Syndrome (ARDS). Management of ARDS is beyond the scope of the present document.

Arterial oxygen saturation should be continuously maintained above 90%. A respiratory rate exceeding 30 breaths per minute is usually a sign of impending ventilatory collapse (18). Evidence based criteria for timely intubation are not available and experience and expertise result in differing opinions. Superiority of one ventilatory strategy to another has not been shown (18) but experts agree that ventilator settings must be adapted to avoid major complications such as volu- and barotrauma.

4. ADJUNCTIVE THERAPEUTIC INTERVENTIONS

4.1 Corticosteroids

Two meta-analyses published in 1995 provided no support for the use of corticosteroids in patients with sepsis or septic shock and even suggested that their use may be harmful (20, 21). However, the studies cited in these meta-analyses were performed between 1963 and 1988 and did not use uniform definitions of septic shock. Brief courses of very high doses methylprednisolone (30 mg/kg) were mostly given.

From a physiopathological viewpoint corticosteroids remain attractive and potentially beneficial drugs in a syndrome characterized by intense inflammation. Reduction of transcription of pro-inflammatory cytokines, an increase in the transcription of IL-1 receptor antagonist, inhibition of the release of adhesion molecules such as ICAM-1 and VCAM-1 and restoration of catecholamine receptors which are desensitised during septic shock are potentially interesting effects of corticosteroids in septic shock. A relative pituitary-adrenal deficit might be present in some patients with septic shock, and correction of this deficit by exogenous steroids might be beneficial.

Two recent prospective, randomised, double-blind single-center placebo-controlled studies, reopened the debate on the use of corticosteroids in septic shock. Bollaert et al. administered 100 mg hydrocortisone tid for 5 days in patients with septic shock (22). Brigel et al. treated patients with a 100 mg bolus of hydrocortisone, followed by 0.18 mg/kg/h. If shock resolved, the dose was reduced to 0.08 mg/kg/h, maintained for 6 days and than progressively tapered (23). Both studies demonstrated a significant improvement in hemodynamic parameters and one showed decreased mortality in the treatment arm (22). Hence, it can not be excluded that moderate ("supraphysiological") doses of hydrocortisone given over a longer period influence the course of septic shock.

4.2 Inflammation modulating strategies ("anti-cytokine therapy")

Several trials with different immune modulating biological agents have been published in the last decade. The disappointing results and the ineffectiveness of all proposed therapies have been extensively discussed and are thought to be due to the complexity of the inflammatory response (the cytokine network), inadequate dosing, inappropriate timing of administration and heterogeneity of studied populations (24-26).

4.3 Immunoglobulins

Beneficial effects of immunoglobulin therapy are thought to arise from an enhanced serum bactericidal activity due to neutralizing and opsonizing IgG and IgM antibodies, as well as stimulation of phagocytosis and neutralization of bacterial endo- and exotoxins. Another possible mode of action might be the immunoglobulin-mediated modification and specific suppression of proinflammatory cytokine release from endotoxin and superantigen activated cells.

Anti-endotoxin antibodies, produced by different methods, have been extensively studied in the late 1980's and early 1990's. All studies yielded disappointing results (24, 25).

Polyvalent IgG or IgM-enriched immunoglobulins have no documented benefit in adult patients with sepsis (27). In contrast, a meta-analysis of 110 cases of *neonatal sepsis* showed a significant decrease in the mortality rate of neonates with sepsis given immunoglobulins. Thus, immunoglobulin therapy should be considered as part of routine therapy in neonatal sepsis (28).

5. GENERAL SUPPORTIVE CARE

5.1 Prevention of venous thrombo-embolism

The incidence of deep venous thrombosis (DVT) in non-surgical ICU patients is about 30% but is probably underestimated. There are no data in the literature with regard to DVT prevention in sepsis or septic shock. However, septic patients have multiple recognized risk factors for DVT: prolonged immobility or paralysis, advanced age, indwelling catheters, major surgery or trauma, underlying malignancy, congestive heart failure, cor pulmonale and a hypercoagulable state. The high incidence of risk factors for venous thromboembolism in septic patients makes prophylaxis warranted.

A significantly decreased incidence of pulmonary embolism and mortality was found in respiratory ICU patients when given low-dose of unfractionated heparin (29).

Major advantages of LMWH (low molecular weight heparins) are once-daily dosing, less and minor bleeding episodes, no need for monitoring, and less heparin-induced thrombocytopenia. They have replaced unfractionated heparine in most Belgian institutions, a practice that is not evidence based yet clinically logical.

Intermittent pneumatic compression has not been studied in critically ill patients. Its use can be considered in those subjects in whom administration of heparin is contra-indicated (18).

5.2 Stress ulcer prophylaxis

Septic patients must be considered at high risk for the development of and bleeding from stress ulcerations, in particular when they require prolonged ventilatory support or in the presence of coagulopathy (30). The keystone measures to the prevention of stress ulceration are early hemodynamic stabilisation, adequate oxygenation, effective analgesia and sedation and prevention of infection. Enteral nutrition, by its gastric pH buffering effect, has also been reported to be an effective preventive measure (31). A meta-analysis showed that stress ulcer prophylaxis with antacids, H_2-receptor antagonists, and sucralfate significantly reduced both overt and clinically important bleeding in critically ill patients and that all drugs did better than placebo (32). The most debated aspect of stress ulcer prophylaxis, in particular with antacids and H_2-blockers, concerns its possible association with ventilator-associated pneumonia. Studies investigating this issue have yielded discordant results due to a large heterogeneity in terms of prophylaxis used, patient population studied, and gastric pH levels obtained. Cook et al. recently reported the results of a multicenter, randomized, blinded trial comparing sucralfate (1 g every 6 hours) with intravenous placebo or ranitidine (50 mg every 8 hours) in 1200 mechanically ventilated patients (33). No difference was found with regard to incidence of ventilator-associated pneumonia and mortality but ranitidine more effectively prevented clinically important gastrointestinal bleeding than sucralfate. Stress ulcer prophylaxis can safely be discontinued in patients without risk factors or organ failure in whom complete intragastric enteral nutrition has been established (34).

5.3 Nutrition

Nutrition studies in general, should look for "hard endpoints" such as long-term survival (e.g. at 6 months) rather than simply focus on short-term end-points with questionable clinical relevance. There is no urgent need for nutritional support during the first 24 to 48 hours in septic shock patients and early nutrition has not been shown to improve outcome (survival) in septic patients (18).

The choice between enteral and parenteral nutrition in critically ill patients is not based on clinical evidence but depends more on intuitive (enteral feeding is more "physiologic"), practical (TPN in case of unaccessible or unusable digestive tract) or economical (enteral feeding is less costly) factors. This question is not relevant for the initial support of septic shock patients. Following adequate resuscitation, most septic patients tolerate intragastric feeding. Prokinetic agents are useful in case of delayed gastric emptying. The role of immunonutrition has firstly to be defined in prolonged critically ill patients before being studied in septic shock patients.

6. CONTINUOUS RENAL REPLACEMENT TECHNIQUES

In addition to a better hemodynamic tolerance and less risk for transient bowel ischemia, another benefit of continuous renal replacement techniques in septic shock patients could be the removal of inflammatory mediators. Studies comparing continuous versus intermittent renal replacement techniques in critically ill patients with acute renal failure reported no difference in survival. It is unlikely that this outcome result would be different if only septic patients had been studied. There is no evidence for a potential role for this technique in the initial (24 to 48 hours) approach of septic shock patients (18, 35).

7. EMPIRICAL ANTIBIOTIC THERAPY IN SEPTIC SHOCK

Inadequate empirical antibiotic therapy results in a statistically significant higher infection-related mortality in bacteremic patients (36). Choice of antimicrobials depends on adequate clinical diagnosis and a knowledge of the most likely pathogens involved and their current resistance pattern. Nosocomial infections are caused by pathogens with increasing resistance in comparison to the pathogens involved in community acquired infection (37). Hence, guidelines for antimicrobial therapy must be guided by recent epidemiologic data, preferably at a local level.

Most authors advocate antimicrobial therapy with beta-lactam antibiotics (third or fourth generation cephalosporins, carbapemens, piperacilline/tazobactam). The superiority of combining beta-lactams with aminoglycosides, even in neutropenic patients, is a matter of disagreement between experts (38). In abdominal sepsis, anti-anaerobic agents must be incorporated in the treatment regimen. Most guidelines published by respected societies are derived from expert panel opinion, mainly based on considerations of epidemiology and assessment of general risk factors (39). These guidelines have not been tested in prospective trials.

8. MONITORING

The criteria for admission to the ICU, the need for routine monitoring such as continuous electrocardiographic monitoring, continuous arterial oxygen saturation measurement (pulse oxymetry), repeated blood lactate determination and other tests are experience and not evidence based. However, in patients requiring vasopressor therapy, invasive blood pressure monitoring should be preferred because measurement using a cuff is frequently inaccurate (5). A pulmonary artery catheter should not be routinely inserted but remains useful to guide therapy in patients unresponsive to fluid resuscitation and vasopressors and in patients with heart failure (40). Other methods to evaluate total body or regional perfusion continue to be investigated and reported. Whether assessment of cardiac performance by echocardiography leads to better outcome than management with central venous or pulmonary pressures monitoring can not be determined at the present time. The utility of gastric tonometry [(yielding a calculated gastric intramucosal pH (pHi)] to guide therapy in septic shock has not been proven (5, 18).

CONCLUSION

In recent years, numerous meta-analyses and consensus conferences addressed the cardiovascular and inflammation modulating therapy in septic shock. We summarized data from these reports and discussed "minor" issues such as respiratory support, prevention of thrombosis and stress ulcer, nutrition, and renal replacement techniques. For these "minor" issues we found conspicuously few valuable studies. This is not unexpected in view of the methodological problems of performing studies in such a complex and difficult to define clinical problem (4). The conclusions of meta-analyses should be cautiously interpreted since meta-analyses predict wrongly the outcome of a randomized controlled trial on the same question in about one third of the cases (41). Our report is not intended to guide new therapeutic strategies but to summarize the currently available, less or more evidence based, treatment options in septic shock patients.

REFERENCES

1. Rosenberg W, Donald A. Evidence based medicine: an approach to clinical problem-solving. *BMJ* 1995; 310: 1122-1126.
2. Sackett DL, Rosenberg WM, Muir Gray JA, et al. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; 312: 71-72.
3. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992; 101: 1644-1655.
4. Vincent JL. Dear SIRS, I'm sorry to say that I don't like you... *Crit Care Med* 1997; 25: 372-374.
5. Task force of the American College of Critical Care Medicine. Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. *Crit Care Med* 1999; 27: 639-660.
6. Boldt J, Muller M, Mentges D, Papsdorf M, Hempelmann G. Volume therapy in the critically ill: is there a difference? *Intensive Care Medicine* 1998; 24: 28-36.
7. Choi PT, Yip G, Quinonez LG, et al. Crystalloids vs colloids in fluid resuscitation: A systematic review. *Crit Care Med* 1999; 27: 200-210.
8. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: sytematic review of randomised controlled trials. *BMJ* 1998; 317: 235-240.
9. Schierhout G, Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. *BMJ* 1998: 316: 961-964.
10. Ernest D, Belzberg AS, Dodek P. Distribution of normal saline and 5% albumin infusions in septic patients. *Crit Care Med* 1999; 27: 46-50.
11. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999; 341: 403-409.
12. American College of Physicians: Practice strategies for elective red blood cell transfusion. *Ann Int Med* 1992; 116: 403-406.

13. Hébert PC, Wells G, Morris A, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; 340: 409-417.
14. Gattinoni L, Brazi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. *N Engl J Med* 1995; 333: 1025-32.
15. Heyland DK, Cook DJ, King D, et al. Maximizing oxygen delivery in critically ill patients: A methodologic appraisal of the evidence. *Crit Care Med* 1996; 24: 517-524.
16. Alía I, Esteban A, Gordo F, et al. A randomized and controlled trial of the effect of treatment aimed at maximizing oxygen delivery in patients with severe sepsis or septic shock. *Chest* 1999; 115: 453-461.
17. Martin C, Papazian L, Perrin G, et al. Norepinephrine or dopamine for the treatment of hyperdynamic septic shock. *Chest* 1993; 103: 1826-1831.
18. Wheeler AP, Bernard GR. Treating patients with severe sepsis. *N Engl J Med* 1999; 340: 207-214.
19. Juste RN, Panikkar K, Soni N. The effects of low-dose dopamine infusions on haemodynamic and renal parameters in patients with septic shock requiring treatment with noradrenaline. *Intensive Care Med* 1998; 24: 564-568.
20. Cronin L, Cook D, Carlet J, et al. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. *Crit Care Med* 1995; 23: 1430-1439.
21. Lefering R, Neugebauer E. Steroid controversy in sepsis and septic shock: a meta-analysis. *Crit Care Med* 1995; 23: 1294-1303.
22. Bollaert PE, Charpentier C, Levy B, et al. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med* 1998; 26: 645-650.
23. Brigel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. *Crit Care Med* 1999; 27: 723-732.
24. Vincent JL. New therapies in sepsis. *Chest* 1997; 115: 330S-338S.
25. Abraham E, Anzueto A, Gutierrez G, et al. Double-blind randomized controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. Norasept II Study Group. *Lancet* 1998; 351: 929-933.
26. Abraham E. Why immunomodulatory therapies have not worked in sepsis. *Intensive Care Med* 1999; 25: 556-566.
27. Werdan K, Pilz G. Supplemental immune globulins in sepsis: a critical appraisal. *Clin Exp Immunol* 1996; 104 (suppl.1): 83-90.
28. Jenson HB, Pollock BH. Meta-analyses of the effectiveness of intravenous immune globulin for prevention and treatment of neonatal sepsis. *Pediatrics*, 1997; 99: E2.
29. Pingleton SK, Bone RC, Pingleton WW, et al. Prevention of pulmonary emboli in a respiratory intensive care unit: Efficiency of low-dose heparin. *Chest* 1981; 79: 647-650.
30. Cook D, Fuller H, Gfuyatt G, et al. Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med* 1994; 330: 377-381.
31. Zandstra DF, Stoutenbeek CP. The virtual absence of stress ulceration related bleeding in ICU patients receiving prolonged mechanical ventilation without any prophylaxis. A prospective cohort study. *Intensive Care Med* 1994; 20: 335-340.
32. Cook DJ, Reeve BK, Guyatt GH, et al. Stress ulcer prophylaxis in critically ill patients. Resolving discordant meta-analyses. *JAMA* 1996; 275: 308-314.
33. Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med* 1998; 338: 791-797.
34. Tryba M, Cook D. Curent guidelines on stress ulcer prophylaxis, Drugs 1997; 54: 581-596.
35. De Vriese AS, Colardyn FA, Lameire NH. Continuous renal replacement therapies in sepsis. Do they matter? In: 1999 Yearbook of Intensive Care and Emergency Medicine, Vincent J-L, Ed, Springer, Berlin, Heidelberg, New York, 611-20.
36. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999; 115: 462-474.
37. Hanberger H, Garcia-Rodriguez JA, Gobernado M, et al. Antibiotic susceptibility among aerobic gram-negative bacilli in intensive care units in 5 European countries. *JAMA* 1999; 281: 67-71.
38. Elting LS, Rubenstein EB, Rolston KVI, Body GP. Outcomes of bacteremia in patients with cancer and neutropenia: Observations from two decades of epidemiological and clinical trials. *Clin Infect Dis* 1997; 25: 247-259.
39. Bartlett JG, Breiman RF, Mandell LA, File TM. Community-acquired pneumonia in adults: guidelines for management. *Clin Infect Dis* 1998; 26: 811-838.
40. Pulmonary artery catheter consensus conference: Consensus statement. *Crit Care Med* 1997; 25: 910-924.
41. Lelorier J, Grégoire G, Benhadded A, et al. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med* 1997; 337: 536-542.