Intensive Care Med (2001) 27: S116–S127

Other supportive therapies in sepsis

Javier Pérez
R. Phillip Dellinger

J. Pérez · R. P. Dellinger (✉)
Division of Cardiovascular and Critical Care Medicine,
Rush-Presbyterian-St. Luke's Medical Center, Chicago, Ill., USA
E-mail: pdelli@rush.edu
Phone: +1-312-942 3330
Fax: +1-312-942 6359

Introduction

Because sepsis is associated with multisystem organ failure, there are many other supportive therapies used to treat these patients that do not directly relate to the sepsis process. Although most of these have been studied in randomized controlled clinical trials in hospitalized patients, few have been tested specifically in sepsis. Thus research and the literature support some, while others are extrapolations from other ill populations.

Deep vein thrombosis (DVT) prophylaxis, nutritional support, and stress ulcer prophylaxis (SUP) are important adjunctive considerations in the management of sepsis. Consumption coagulopathy makes the septic patient at risk for development of venous clots. Nutritional support, especially enteral, is recognized as important in supporting the critically ill septic patient who is unable to eat. In addition, sepsis and the associated organ dysfunction put the patient at increased risk for development of stress ulcers.

Methods

We performed a comprehensive Medline literature search from January 1966 to February 2000. The following terms were independently searched: DVT, deep vein thrombosis, thrombophlebitis, venous thrombosis, thromboembolic disease, pulmonary embolism, anticoagulation, warfarin, heparin, low-molecular weigh heparin, DVT prophylaxis, mechanical compression devices, external pneumatic compression, nutritional support, parenteral nutrition, total parenteral nutrition, enteral nutrition, immunoenhancing diets, immunomodulating diets, stress ulcers, gastrointestinal bleeding, SUP, gastrointestinal bleeding prophylaxis, gastrointestinal bleeding prevention, antacids, histamine antagonists, sucralfate, antiulcer agents, omeprazole, and proton-pump inhibitors.

Each one of those terms was searched and crossed with the following: critical care, intensive care, infection, systemic inflammatory response syndrome, sepsis, severe sepsis, sepsis syndrome, septic shock, and multiple organ dysfunction syndrome.

Deep vein thrombosis prophylaxis in sepsis

The use of DVT prophylaxis in higher risk postoperative patients has been universally accepted since the early 1970s when it was found to reduce the risk of thromboembolic phenomena in this group [1]. Many subsequent trials have continued to emphasize the value of DVT prophylaxis in most postoperative patients [2, 3, 4, 5]. In addition to postoperative patients, subcutaneous heparin has also proven efficacious in reducing the risk of thromboembolism among myocardial infarction [6, 7, 8, 9] and ischemic stroke patients [10, 11, 12]. Only a few studies of venous thromboembolism prophylaxis have been carried out on general medical wards, and medical intensive care units. In those studies, patients treated with subcutaneous heparin [13, 14, 15, 16, 17] or with low molecular weight heparin (LMWH) [18, 19] reduced the risk of thromboembolic events.

Does DVT prophylaxis improve clinical outcome in patients with sepsis?

Answer: yes, grade A.

Recommendations

Considering the frequent occurrence of independent risk factors for DVT in septic patients and the high per-

Table 1 DVT prophylaxis studies performed in general populations of the acutely ill: percentage of sepsis/infected patients

Reference	Design, methods	Setting	*n*	Infection, sepsis *n*	%	Results
Pingleton et al. [13]	Prospective/historical controls, V/Q angio, autopsy	Respiratory care unit	188	53	28	Reduction in incidence of pulmonary embolism
Cade [14]	Prospective, double-blind placebo-control, I-fibrinogen scan	ICU/medical ward	119/131	ND	–	Reduction in incidence of DVT (29% vs. 13%)
Halkin et al. [15]	Randomized prospective control, no data	Medical ward	1358	138	10	Reduction in mortality (10.9% vs. 7.8%)
Belch et al. [16]	Prospective randomized, control, I-fibrinogen scan	ICU	100	52	52	Reduction in incidence of DVT (26% vs. 4%)
Gardlund et al. [17]	Prospective randomized, no data	Medical ward	11693	1610	14	Minor thromboembolic events reduced
Samana et al. [18]	Placebo-control, double-blind, randomized, venography, ultrasound, V/Q angio, CAT, autopsy	Medical ward/ ICU	1102	584	53	Reduction in incidence of DVT (14.9% vs. 5.5%)
Dahan et al. [19]	Placebo-control randomized, I-fibrinogen	Medical ward	270	11	4	Reduction in incidence of DVT (9% to 3%)

centage of sepsis/infected patients included in studies that have demonstrated efficacy of DVT prophylaxis in general, septic patients should be treated with DVT prophylaxis. Even though there is not a randomized study that establishes the impact of DVT prophylaxis on morbidity and mortality specifically in septic patients, the significant number of septic patients included in the populations of patients enrolled in other prospective randomized trials supports that the use of DVT prophylaxis reduces morbidity and mortality in septic patients. Moreover, septic patients, especially those with severe sepsis and multiple organ failure, have less cardiopulmonary reserve, and the impact of a minor thromboembolic event in this group of patients could be very compromising.

Rationale

Patients in the intensive care unit are at high risk of development of thromboembolic phenomena [14, 20, 21]. Septic patients as described above are expected to be in the intensive care unit (ICU) and to be part of the population at risk. No definitive study restricted to the incidence of DVT in septic patients has been carried out. The significance of DVT prophylaxis on morbidity and mortality in septic patients needs to be implied based on the analysis of proportion of the septic patients included in the studies of the acutely ill patient in general (Table 1). Pingleton et al. [13], observed a reduction in the incidence of pulmonary embolism in patients admitted to the respiratory intensive care unit. Cade [14] found a reduction in the risk of thromboembolic events from 29% to 13% among patients admitted to ICU and treated with subcutaneous heparin. In the latter study, using a control group consisting of patients admitted to the medical ward and coronary care unit, a significantly higher incidence of thromboembolic events was found among patients admitted to the ICU. Halkin and coworkers [15], in a randomized prospective study of patients admitted to medical wards, compared treatment with low-dose unfractionated heparin to patients who did not receive any treatment. They found a significant reduction in mortality in heparin-treated patients (7.8% vs. 10.9%). Belch et al. [16], in a study carried out in medical patients admitted to the intensive care unit, found a significantly reduced incidence of thromboembolic events (4% vs. 26%) in the group treated with unfractionated heparin.

Mortality was not addressed in the study. Gardlund et al. [17], found a significant reduction in minor embolic events in patients admitted to the hospital with infectious disease diagnoses who were treated with subcutaneous heparin versus those not treated, although there was no difference in mortality or major thromboembolic events. In a recently published trial [18] 1102 patients received either LMWH (in two different doses) or placebo. Although the patients included in this trial were not admitted to the ICU, many of them suffered from complicated conditions. Patients receiving 40 mg enoxaparin had a significant reduction in the incidence of thromboembolic phenomena (5.5% vs. 14.9%). No significant difference was found in mortality among any of the groups, but a trend toward decreased mortality in

patients receiving 40 mg enoxaparin was reported. Dahan et al. [19] compared medical patients using treatment with LMWH versus placebo in a double-blind, placebo-controlled randomized trial. LMWH reduced the incidence of thromboembolic phenomena (9.1% vs. 3%). Hirsch and colleagues [20] studied 100 patients admitted to ICU and found the incidence of DVT to be 33%. There was an association with increased mortality in patients suffering DVT (although it is not possible to determine whether death was caused by DVT or was a consequence of the deteriorated state of those patients). Although it is difficult to demonstrate mortality benefit from DVT prophylaxis unless either a very large study or patients at very high risk are studied, many argue that demonstrating a decrease in DVT without increase in bleeding complications implies that mortality benefit could be demonstrated if higher powered studies were performed.

Septic patients, especially those admitted to the ICU, frequently have one or more risk factors for thromboembolic phenomena. These have been widely described in postoperative, medical and critically ill patients [14, 22, 23, 24.]. These factors are: age (> 40 years), history of venous thromboembolism, malignancy, bed rest (> 5 days), major surgery, congestive heart failure, fracture (pelvic, hip or leg), estrogen replacement, stroke, myocardial infarction, multiple trauma, and hypercoagulable states. The concurrence of two or more factors increases the risk of thromboembolic events [23, 24]. Other risk factors frequently present in septic patients include use of central venous catheters [20, 25, 26, 27], use of neuromuscular blockade, use of deep sedation [28], and presence of coagulopathy [29].

Is there any pharmacological method for DVT prophylaxis preferred in septic patients?

Answer: no, grade A.

Recommendations

Septic patients who do not have a contraindication to heparin use should receive prophylaxis with either low-dose unfractionated heparin (5,000 U either two or three times daily) or LMWH (at recommended doses; grade A). For those septic patients who have an absolute contraindication for heparin use (i.e., thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage), the use of a mechanical prophylactic device is advised since this method has proven to be effective in postsurgical patients and therefore would likely work in septic patients (grade E).

Rationale

Unfractionated subcutaneous heparin (UH) is widely used for the prevention of DVT among postoperative patients and in medical high-risk patients. UH is inexpensive and has been demonstrated in critically ill medical and surgical patients to be safe and to be associated with minor bleeding complications (bruising, hematoma at the site of injections) and rarely with heparin-induced thrombocytopenia [13, 14, 24, 30, 31].

Although smaller studies have suggested that LMWH may be either as effective as UH with less bleeding complications or more effective with the same bleeding complications [31, 32, 33] in the treatment of thromboembolic disease, larger studies have not demonstrated statistically significant differences between the drugs. However, LMWH has been demonstrated to be more effective than UH in several high-risk populations for prophylaxis of DVT [34]. Enoxaparin has been demonstrated to be safe and efficacious in treatment of thromboembolic disease in medical patients with minimal adverse events [18]. Two other randomized studies [35, 36, 37] in acutely ill medical patients compared LMWH and UH and showed equal effectiveness in the prevention of DVT. Each hospital should assess which form of heparin is most cost effective at that institution. Both are effective in presenting DVT in at-risk patients.

Special considerations: patients with sepsis-induced coagulopathy

Sepsis is frequently associated with hemostatic defects [29, 40]. The sepsis milieu may include consumptive coagulopathy and liver dysfunction leading to predisposition for both clotting and bleeding. Thrombocytopenia is frequently present in septic patients. In the setting of active hemorrhage or in septic patients with significant abnormality in clotting function we recommend the use of mechanical leg compression devices as a preferred alternative to heparin. Intermittent pneumatic compression devices applied to legs have been demonstrated to be efficacious in postoperative patients [38, 39], and the use of these devices is recommended in septic patients with contraindication to the use of heparin (grade E).

Nutrition in sepsis

Septic patients are characterized by having increased energy expenditure and enhanced catabolism [41, 42]. The need to provide adequate nutritional support to septic patients is thus generally accepted as part of standard care in the ICU. However, many issues regarding nutrition to septic patients remain controversial. This controversy is enhanced by the fact that most nutritional

data available come from studies performed in trauma or postsurgical patients, as opposed to a population of septic patients alone.

Does institution of nutritional support improve clinical outcome of patients with sepsis?

Answer: yes, grade E

Recommendations

Based on the assumption that sepsis produces a hypercatabolic state and leads to protein-energy malnutrition, and given that protein loss is associated with poor outcome, nutritional support in septic patients is recommended. The correlation of nutritional support with outcome in septic patients comes from data extrapolated from studies performed in perioperative patients and from expert opinion that allow us to establish this recommendation. Many important questions remain regarding what kind of nutrition and when in the course of sepsis should nutrition begin.

Rationale

Nutritional status has been closely related with outcome of critically ill patients. Malnutrition has been associated with increased morbidity and longer hospital stays [43]. Mullen et al. [44] in 1980 demonstrated a reduction in perioperative complications in surgical patients with the use of adequate nutritional support. Scientific evidence supports the important role of nutritional status in the outcome of septic and other critically ill patients [45, 46, 47]. Decreased gastrointestinal mucosal permeability [48], improved healing function [49], and lower infection rates [47] have been attributed to the use of enteral feeding in critically ill patients.

The activation of the inflammatory cascade in sepsis alters the body's metabolism. Patients with sepsis have elevated energy requirements, net catabolism, and rapid loss of lean mass [50, 51]. For this reason the use of nutritional support has been axiomatically accepted. The ability of nutrition to alter the clinical outcome of critically ill patients, however, is controversial [52, 53]. Studies have identified enteral nutrition as a major factor in maintaining normal gut mucosal function [48, 54], both in humans and in animals. Thus the use of enteral formulas would be expected to maintain mucosal integrity in the critically ill septic patient. Most of the studies investigating metabolic changes and effects of nutrition have been carried out in postoperative patients and have provided conflicting conclusions. For example, one study demonstrated a direct relationship between body mass index and mortality in critically ill patients [55] whereas another placebo-controlled study demonstrated no difference in clinical outcome between patients receiving enteral nutrition and those receiving intravenous crystalloid [56].

Are there any nutritional routes or formulations preferred for patients with sepsis?

Answer: yes, grades C, E, B (based on different populations)

Recommendations

Enteral nutrition is the preferred method of nutritional support in the catabolic critically ill patient in general, inclusive of the septic patient (grade C). For those patients who cannot tolerate enteral nutrition for a prolonged time or when contraindications do not allow its use (mesenteric ischemia, mechanical bowel obstruction), parenteral nutritional support should be used (grade E). Immune-enhancing formulas may be better than other enteral formulations in critically ill patients, but effects on ultimate outcome (i.e., survival) remain to be demonstrated in large randomized trials (grade B).

Rationale

Although controversy exists, most authorities advocate the use of enteral nutrition in critically ill patients [57, 58]. Several studies have compared enteral and parenteral nutrition in critically ill patients, most of them perioperative. Cerra and coworkers [53] compared standard nutrition with total parenteral nutrition in septic patients. No difference was found in clinical outcome.

However, enteral nutrition has proven superior to parenteral nutrition in reduction in stress ulcers [59], gut protection [48], and costs [52, 60]. In addition, catheter placement and indwelling catheters have been associated with increased complications [61, 62]. A recent meta-analysis [47] found an increased rate of complications and mortality in ICU medical patients receiving parenteral nutrition when compared with those receiving enteral feeding. The advantage of enteral nutrition versus total parenteral nutrition in some high-risk groups has been demonstrated [63, 64].

Recent studies have also examined the potential advantage of enriched mixtures of enteral feeding formulas compared with standard formulas [50, 65, 66, 67, 68]. Bower et al. [50], published a prospective randomized clinical trial in septic patients comparing standard enteral feeding versus an immunomodulatory formula that contained arginine, nucleotide, and fish oil.

Although mortality was not modified, a significant reduction in length of stay and infections was noted in the immunomodulatory formula group. Galbán and coworkers [67] concluded a benefit of immune-modulatory diets in septic patients from their study which revealed a decrease in mortality from 32 % to 19 %, and in infection from 20 % to 7 %. Atkinson and colleagues [68] published a controlled double-blind clinical trial involving medical and surgical ICU patients. They compared different formulations of enteral nutrition. The use of immunomodulatory formula reduced mechanical ventilation time, ICU stay, hospital length of stay and duration of systemic inflammatory response syndrome. A recent study by Gadek et al. [69] in patients with acute respiratory distress syndrome, including a proportion of septic patients, resulted in significant differences in outcome in those patients who received an immunomodulatory diet.

Are there any preferred range of calories and/or proportion of elements in nutritional support in sepsis?

Answer: yes, grade E

Recommendations

The following are specific recommendations for septic patients, according to the guidelines established by the American College of Chest Physicians [58] and American Society of Parenteral and Enteral Nutrition [70] consensus conferences:

- Daily caloric intake: 25–30 kcal/kg usual body weight
- Protein: 1.3–2.0 g/kg per day
- Glucose: 30–70 % of total nonprotein calories, to maintain serum glucose level below 225 mg/dl
- Lipids: 15–30 % of total nonprotein calories. ω6-Polyunsaturated fatty acid should be reduced in septic patients, maintaining that level which avoids deficiency of essential fatty acids (7 % of total calories – generally 1 g/kg per day).

No specific recommendations are offered for use of medium-chain triglycerides, branched-chain amino acids, or specific microelements added to the nutritional formulas. The use of any of these strategies, although supported in concept, does not have enough investigational evidence to determine any clinical benefit in outcome of septic patients.

Rationale

No randomized clinical trial has addressed optimal total caloric requirements or the amount of fat and protein needed in the diet of septic patients. Much of our knowledge regarding these issues derives from studies carried out in patients with trauma, burns, and surgery, who, as in the case of septic patients, are frequently hypercatabolic. Despite a lack of clinical outcome evidence from randomized trials, expert panels have offered recommendations for general critically ill patients and for septic patients as well.

In 1993 the American Society of Parenteral and Enteral Nutrition used an evidence-based approach to publish practice guidelines for nutritional support in the ICU [70]. Although the guidelines do not address specific recommendations for septic patients, they provide a grade B recommendation for total caloric requirements in critically ill patients. In presenting the results of a more recent conference the authors emphasize the use of branched-chain amino acids in the composition of enteral formulas although the existing data did not allow establishing specific recommendations [71]

The American College of Chest Physicians (ACCP) in 1997 published a consensus statement of nutrition guidelines in ICU patients [58]. Specific recommendations on caloric requirements in septic patients as well as proportion of nutrients in formulations were offered. Since then these recommendations have found agreement by most experts, but large gaps remain in our scientific basis for recommending enteral feeding in the short-term critically ill patient [72, 73, 74].

Stress ulcer prophylaxis in sepsis

The use of SUP to prevent upper gastrointestinal bleeding in critically ill patients has become a routine in the ICU. However, there are controversial points in this practice: (a) SUP has not demonstrated a benefit in mortality [23]; (b) there are many definitions of upper gastrointestinal bleeding in critically ill patients that could be responsible for the heterogeneity in results in several controlled studies [75, 76]; (c) the use of SUP has been implicated in the development of ventilator-associated pneumonia although the impact of this complication on mortality and morbidity has not been established [77, 78]; (d) only specific subgroups of patients in the ICU are likely to benefit from SUP [79].

Comparing the various studies is made difficult by the varied criteria used for diagnosing stress ulcer bleeding. The use of microscopic bleeding (either orthotoluidine or guaiac in nasogastric aspirate or feces) as a marker of stress ulcer bleeding entails several problems that have already been identified: (a) guaiac is

Table 2 Proportion of septic patients in different studies of SUP (*R* randomized trial, *P* placebo, *C* control, *SU* stress ulcer, MV mechanical ventilation)

Study	Trial	*n*	Septic patients (%)	Sepsis definition	Summary of results
Cook et al. [79]	Cohort	2252	1.6	Fever-hypothermia, leukocytosis/leukopenia, + blood culture	Risk factors for SU bleeding: prolonged MV and coagulopathy
Schuster et al. [82]	Cohort	179	7.8	Not listed	Risk factors for SU bleeding: coagulopathy, hypotension and MV
Zandstra and Stoutenbeek [83]	Cohort	167	40	Severe bacterial infection	Minimal SU bleeding episodes; prolonged MV identified as a risk factor
Pinilla et al. [84]	R-C	259	3.8	2 criteria of: fever; WBC > 15,000, shift to the left, + culture	No difference between patient treated with antacids and control
Peura and Johnson [85]	R/P-C	39	15	Not listed	Cimetidine superior to placebo in preventing SU; fewer transfusions required in treated group
Groll et al. [86]	R/P-C	221	30–15[a]	Not listed	No significant differences between placebo and cimetidine
Basso et al. [87]	R/C	168	22	Foci of infection or septicemia and fever, leukocytosis, elevated sed rate and culture +	Cimetidine and antacid decreased the risk of SU bleeding compared to placebo
Ben-Menachem et al. [88]	R/C	300	21	Not listed	No differences between cimetidine and sucralfate vs. control
Borrero et al. [89]	R	155	30	Not listed	No differences between sucralfate and antacids
Bressalier et al. [90]	R	74	23	Systemic infection with + cultures or hypotension	Sucralfate advantages vs. antacids (both in safety and effectiveness)
Cook et al. [91]	R	1200	6.5	Not listed	Ranitidine offers better protection than sucralfate; no differences in ventilator-associated pneumonia
Poleski and Spanier [92]	R	37	45	Blood culture with evidence of infection (fever, leukocytosis)	Cimetidine and antacids equally effective
Stothert et al. [93]	R	123	28	Culture and clinical evidence; sepsis confirmed at autopsy or surgery	Antacids and cimetidine equally effective

[a]Referred to 30% of septic patients in the placebo group and 5% in the cimetidine group

nonspecific [80]; (b) cimetidine may produce false-positive results in gastric aspirates [81]; (c) the clinical relevance of microscopic bleeding is usually minimal, and a minority of cases progress toward overt or clinically significant bleeding. The use of overt bleeding (hematemesis, gross blood, or coffee ground material in nasogastric aspirates, hematochezia, or melena) or clinically important bleeding (associated with a decrease in systolic blood pressure > 20 mmHg, orthostatic changes, decrease in hemoglobin > 2 g/dl, transfusion of at least 2 U blood in 24 h caused by the bleeding episode, or the need of surgical intervention) seems more reasonable when evaluating the impact of stress ulcers in morbidity and mortality and the efficacy of the prophylactic measures.

Although there are no specific studies of SUP in septic patients, many randomized trials have been carried out in critically ill patients that include some number of septic patients. Unfortunately, only few studies do allow identification of the precise number of septic patients enrolled (Table 2 lists the proportion of septic patients in prospective studies). Furthermore, it is possible to compare the frequency of occurrence of stress ulcer bleeding in septic patients with that of patients at higher

risks, because many of the risk factors for development of stress ulcer bleeding are common in septic patients.

Does SUP improve clinical outcome in patients with sepsis?

Answer: yes, grade C

Recommendations

No randomized trial has evaluated the effect of SUP on clinical outcome in septic patients. Examination of successful clinical trials of SUP does not allow precise identification of patients with diagnosis of sepsis. Therefore no definitive data exist in septic patients on the effectiveness of SUP in diminishing episodes of overt or clinically significant bleeding. The clinical utility of SUP as it affects clinical outcome in septic patients is therefore not clear. Septic patients have been assumed to have an increased risk for SUP since they have multiple risk factors known to increase the risk of stress ulcer bleeding. Since data do support SUP as being efficacious in preventing upper gastrointestinal bleeding in populations of critically ill patients, which would be expected to contain large proportions of septic patients, the use of SUP is recommended in this group (see below).

Rationale

The use of SUP has become accepted practice in the great majority of ICUs. Early studies associated sepsis with stress ulcer bleeding and with an increased risk of mortality in critically ill patients [94]. The initial study by Skillman et al. [94] retrospectively reported a mortality of 87 % in patients admitted to the ICU (medical and surgical) who developed stress ulcer related gastrointestinal bleeding. The use of SUP has become accepted practice in the great majority of ICUs. However, recent studies report significantly less mortality related to stress ulcer bleeding [79, 83, 91]. Schuster et al. [82] reported a 14 % incidence of bleeding in patients admitted to a respiratory intensive care unit. Although the mortality was significantly higher among patients who bled (64 % vs. 9 %), death was related to bleeding only in 3 of the 25 patients who bled. Other studies [85, 95] comparing histamine receptor antagonists or antacids versus placebo report similar results. Moreover, several authors believe that the modernization of anesthesia and ventilation techniques and, in general, the improvement in the management of critically ill patients have decreased the incidence of stress ulcers and therefore prophylaxis is not warranted [79, 80, 81, 82, 83]. Lacroix and colleagues [96] in a meta-analysis observed a range of overt bleeding from 1.6 % to 52.8 % of in control groups and from 0 to 23.1 % in antacids groups. The conclusion of the study was that cimetidine and antacids are effective in preventing stress ulcer bleeding (33 % and 43 % better than control, respectively).

Collectively these studies support the assertion that patients who develop bleeding from stress ulcers require more transfusions. However, no difference in clinical outcome has been noted. Patients with stress ulcer bleeding who do not receive SUP often show two factors: coagulopathy and liver failure. A recent meta-analysis [97] reporting risk reduction for bleeding in critically ill patients with antacids, sucralfate, or histamine-2 receptor antagonists could not establish any impact on clinical outcome compared with control groups. Ben-Menachem et al. [88], in a randomized single-blind, control trial, reported that the incidence of bleeding did not differ among three groups of 100 patients (control, sucralfate, and cimetidine). The mortality and hospital length of stay did not vary with prophylaxis.

Is there any specific subgroup of septic patients who should receive SUP?

Answer: yes, grades A, C

Recommendations

Although no large randomized trial has addressed septic patients alone, abundant data exist regarding subgroups of septic patients with prolonged mechanical ventilation, hypotension, and coagulopathy. For these patients the use of SUP is recommended (grade A). For other septic patients in whom these factors are not present SUP is recommended based on several small randomized trials in which SUP has proven efficacious in preventing bleeding and therefore reducing morbidity in critically ill patients (grade C).

Rationale

Cook et al. [79] in a prospective study found an increased risk of stress ulcer bleeding in patients with prolonged mechanical ventilation (> 48 h) and those with coagulopathy. The low number of septic patients in this study does not allow the determination of the true impact of sepsis as an independent risk factor for the development of stress ulcer bleeding. Schuster et al. [82] found increased risk of bleeding associated with coagulopathy, prolonged mechanical ventilation, and sepsis. The authors of this study did not perform a multivariate analysis that would help to determine the true impact of sepsis as a single variable risk factor for stress ulcer

bleeding. Coagulopathy, frequently found in severe sepsis, has been classically associated with increased incidence of bleeding [98]. Risk factors for stress ulcer bleeding have been demonstrated to be additive [95, 96, 97, 98, 99]. A score has been offered to predict the risk of SU bleeding [100].

Are some methods to be preferred over others in the prevention of stress ulcers in patients with sepsis?

Answer: uncertain, grade B.

Recommendations

Several trials have confirmed the efficacy of antacids, sucralfate, or histamine-2 receptor antagonists in preventing stress ulcer bleeding. Since the data are conflicting, no single one can be determined as preferable. General recommendations should be based on the individual experience in the use of one or another, the availability, or cost-analysis in individual centers. In septic patients with risk factors the use of enteral nutrition following the preventive strategies currently available may be beneficial for preventing stress ulcer bleeding.

Rationale

There are many studies comparing the efficacy of histamine-2 receptor antagonists, antacids, and sucralfate in the prevention of stress ulcer bleeding [85, 86, 87, 88, 90, 100, 101, 102]. Cook et al. [103] in a meta-analysis of SUP studies found histamine-2 receptor antagonists more effective than antacids in controlling overt bleeding. No data about nosocomial pneumonia were presented. There was no difference in mortality between the three methods, and no difference was found when compared with no prophylaxis. Similar results have been reported by two other meta-analysis [96, 97]. A controversy related to SUP stems from the ability of both antacids and histamine-2 receptor antagonists to raise the gastric pH, which may be associated with increase in gastric bacterial colonization. Increased bacterial presence in the gastrointestinal tract can lead to an increase in pneumonia if it is a route that leads to pharyngeal colonization. This area is controversial, and although some studies have demonstrated an increase in ventilator-associated pneumonia with the use of histamine-2 blockers and antacids, these data have not been validated in all clinical trials [77, 91, 103]. Furthermore, prospective studies suggest that gastric colonization is not a frequent route to pharyngeal colonization [104]. In a recently published Canadian trial [91] the risk of bleeding (in 1200 patients studied) was significantly less in patients treated with ranitidine, without increased associated pneumonia. These findings have been corroborated in other studies [105, 106]. A meta-analysis published in 1996 found sucralfate to be associated with a trend toward a lower incidence of pneumonia compared with both antacid and histamine-2 receptor antagonists. In this meta-analysis sucralfate was associated with less mortality. A recently published cost effectiveness analysis [107] pointed out the high costs involved in SUP. In 1999 a national survey in the United States [108] found a wide variation in the forms of SUP among intensivists. The costs of prophylaxis in low-risk patients were considered by these authors as prohibitive. In this survey the authors called for the creation of hospital-based algorithms, based on individualization of cost and care issues at the institution as it applies to patients with higher risks of bleeding.

There are also data supporting the use of enteral nutrition as SUP [59]. The beneficial effect of enteral feeding has been demonstrated with distal enteral nutrition rather than gastric. Patient's position, type of tube (orogastric versus nasogastric, small-bore versus large-bore), and continuous versus intermittent delivery, are factors implicated by the findings of various studies that could modify stress ulcer bleeding in patients receiving enteral nutrition [109].

Summary

Patients who survive the circulatory and organ deficits in sepsis may still fall victim to complications such as pulmonary embolism and stress ulcer bleeding. Although there is no clearcut evidence to quantitate the impact of such complications on mortality, the anticipated impact is grave when considering the compromised physiological reserve of these patients. For this reason it is important to institute effective prophylaxis to minimize the impact. In addition, catabolism associated with sepsis likely influences the recovery of patients with sepsis and moreover can compromise the response of the immune system against an infectious insult. Early and adequate nutritional support therefore appears important. There is much controversy and lack of prospective research regarding effect of supportive therapies on outcome in patients with severe sepsis. This research is needed.

References

1. Kakkar VV, Corrigan TP, Fossard DP and the International Multicentre Trial (1975) Prevention of fatal postoperative pulmonary embolism by low doses of heparin: an international multicentre trial. Lancet II:45–51
2. Upchurch GR, Demling RH, Davies J, Gates JD, Knox JB (1995) Efficacy of subcutaneous heparin in prevention of venous thromboembolic events in trauma patients. Am Surg 61: 749–755
3. Fauno P, Suomalainen O, Rehnberg V, Hansen TB, Kroner K, Soimakallio S, Nielsen E (1994) Prophylaxis for the prevention of venous thromboembolism after total knee arthroplasthy. J Bone Joint Surg Am 76: 1814–1818
4. Amstutz HC, Friscia DA, Dorey F, Carney BT (1989) Warfarin prophylaxis to prevent mortality from pulmonary embolism after total hip replacement. J Bone Surg Am 71: 321–326
5. Fisher CG, Blachut PA, Salvian AJ, O'Brien PJ (1995) Effectiveness of pneumatic leg compression devices for the prevention of thromboembolic disease in orthopaedic trauma patients: a prospective, randomized study of compression alone versus no prophylaxis. J Orthop Trauma 9: 1–7
6. Medical Research Council (1969) Assessment of short-term anticoagulant administration after cardiac infarction. BMJ 1: 335–e42
7. Drapkin A, Merskey C (1972) Anticoagulant therapy after acute myocardial infarction. JAMA 222: 541–548
8. Warlow C, Beattie AG, Terry G, Ogston D, Kenmure ACF, Douglas AS (1973) A double-blind trial of low doses of subcutaneous heparin in the prevention of deep vein thrombosis after myocardial infarction. Lancet II: 934–936
9. Kierkegaard A, Norgren L (1993) Graduated compression stockings in the prevention of deep vein thrombosis in patients with acute myocardial infarction. Eur Heart J 14: 1365–1368
10. Prins MH, Gelsena R, Sing AK, van Heerde LR, den Ottolander GJ (1989) Deep vein thrombosis prophylaxis with a low molecular weight heparin in stroke patients. Haemostasis 19: 245–250
11. McCarthy ST, Turner JJ, Roberston D, Hawkey CJ, Macey DJ (1977) Low dose heparin as prophylaxis against deep vein thrombosis after acute stroke. Lancet II:800–801
12. Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, Andrew M, Magnani HN, Hull RD, Gent M (1987) A double blind randomized trial of ORG 10172 low molecular weight heparinoid in the prevention of deep vein thrombosis in thrombotic stroke. Lancet I:523–526
13. Pingleton SK, Bone RC, Pingleton WW, Ruth WE (1981) Prevention of pulmonary emboli in a respiratory intensive care unit. Chest 79: 647–650
14. Cade JF (1982) High risk of the critically ill for venous thromboembolism. Crit Care Med 10: 448–450
15. Halkin H, Goldberg J, Modan M, Modan B (1982) Reduction in mortality in general medical in-patients by low-dose heparin prophylaxis. Ann Intern Med 96: 561–565
16. Belch JJ, Lowe DO, Ward AG, Forbes CD, Prentice CRM (1981) Prevention of deep vein thrombosis in medical patients by low-dose heparin. Scott Med J 26: 115–117
17. Gardlund B and the Heparin Prophylaxis Study Group (1996) Randomized, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases. Lancet 347: 1357–1361
18. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, Leizorovicz A, Nguyen H, Olsson CG, Turpie AG, Weisslinger N (1999) A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med 341: 793–800
19. Dahan R, Houlbert D, Caulin C, Cuzin C, Viltart C, Woler M, Segrestaa JM (1986) Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: a randomized double-blind trial. Haemostasis 16: 159–164
20. Hirsch DR, Ingenito EP, Goldhaber SZ (1995) Prevalence of deep venous thrombosis among patients in medical intensive care. JAMA 274: 335–337
21. Gallus AS, Hirsh J, Tuttle RJ, Trebilcock R, O'Brien S, Carroll JJ, Minden JH, Hudecki S (1973) Small subcutaneous doses of heparin in prevention of venous thrombosis. N Engl J Med 288: 545–551
22. Thromboembolic Risk Factors Consensus Group (1992) Risk of and prophylaxis for venous thromboembolism in hospital patients BMJ 305: 567–574
23. Saint S, Matthay M (1998) Risk reduction in the intensive care unit. Am J Med 105: 515–523
24. Anderson FA, Wheeler HB (1995) Venous thromboembolism. Risk factors and prophylaxis. Clin Chest Med 16: 235–251
25. Wheeler HB, Anderson FA Jr, Cardullo PA, Patwardhan NA, Jian-Ming L, Cutler BS (1982) Suspected deep vein thrombosis: management by impedance plethysmography. Arch Surg 117: 1206–1209
26. Randolph AG, Cook DJ, Gonzales CA, Andrew M (1998) Benefit of heparin in central venous and pulmonary artery catheters. A meta-analysis of randomized controlled trials. Chest 113: 165–171
27. Borow M, Crowley JG (1985) Evaluation of central venous catheter thrombogenicity. Acta Anaesthesiol Scand 81 [Suppl]:59S–64S
28. Durbec O, Viviand X, Potie F (1997) Lower extremity deep vein thrombosis: a prospective, randomized, controlled trial in comatose or sedated patients undergoing femoral vein catheterization. Crit Care Med 25: 1982–1985
29. Carvalho AC, Freeman NJ (1994) How coagulation defects alter outcome in sepsis: survival may depend on reversing procoagulant conditions. J Crit Illness 9: 51–75
30. Clagett GP, Reisch JS (1988) Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. Ann Surg 208: 227–240
31. Levine MN, Raskob G, Landfield S, Hirsh J (1995) Hemorrhagic complications of anticoagulant treatment. Chest 108 [Suppl]:276S–290S
32. Warkentin TE, Levine MN, Hirsh J (1995) Heparin induced thrombocytopenia in patients treated with low molecular weight heparin or unfractionated heparin. N Engl J Med 332: 1330–1335
33. Hirsh J, Raschke R, Warkentin, Dalen JE, Poller L (1995) Heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. Chest 108 [Suppl]:258S–275S
34. Green D, Hirsh J, Heit J, Prins M, Davidson B, Lensing AWA (1994) Low molecular weight heparin: a critical analysis of clinical trials. Pharmacol Rev 46: 89–121

35. Bergman JF, Neuhart E (1988) A multicenter randomized, double-blind study of enoxaparin compared with unfractionated heparin in the prevention of venous thromboembolic disease in elderly in-patients bedridden for an acute medical illness. Thromb Haemost 60: 407–410
36. Haremberg J, Kallenbach B, Martin CE, Dempfle E, Zimmermann R, Kübler W, Heene DL (1990) Randomized controlled study of heparin and low molecular weight heparin for prevention of deep-vein thrombosis in medical patients. Thromb Res 59: 639–650
37. Simmonneau G, Sors H, Charbonnier B, Page Y, Laaban JP, Azarian R, Laurent M, Hirsch JL, Ferrari E, Bosson JL, Mottier D, Beau B (1997) A comparison of Low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. N Engl J Med 337: 663–669
38. Anglen JO, Goss K, Edwards J (1998) Foot pump prophylaxis for deep vein thrombosis: the rate of effective usage in trauma patients. Am J Orthop 27: 580–582
39. Black PM, Crowell RM, Abbott WM (1986) External pneumatic calf compression reduces deep thrombosis in patients with ruptured intracranial aneurysms. Neurosurgery 18: 25–28
40. Mammen EF (1994) Coagulation defects in liver disease. Med Clin North Am 78: 545–553
41. Cerra FB, Siegel JH, Coleman B (1980) Septic autocanibalism: a failure of exogenous nutritional support. Ann Surg 192: 570–580
42. Bartlett RH, Dechert RR, Mault JR, Ferguson SK, Kaiser AM, Erlandson EE (1982) Measurement of metabolism in multiple organ failure. Surgery 92: 771–779
43. Dempsey DT, Mullen JL, Buzby GP (1988) The link between nutritional status and clinical outcome: can nutritional intervention modify it? Am J Clin Nutr 47: 351–356
44. Mullen JL, Busby GP, Matthews DC, Smale BF, Rosato EF (1980) Reduction of operative morbidity and mortality by combined pre-operative and post-operative nutritional support. Ann Surg 192: 604–613
45. Young B, Ott L, Twyman D, Norton J, Rapp R, Tibbs P, Haack D, Brivins B, Dempsey R (1987) The effect of nutritional support on outcome from severe head injury. J Neurosurg 67: 668–676
46. Border JR, Hasset J, LaDuca J, Seibel R, Steinberg S, Mills B, Losi P, Border D (1987) The gut origin septic states in blunt multiple trauma in the ICU. Ann Surg 206: 427–448
47. Moore FA, Feliciano DV, Andrassy RJ (1992) Early enteral feeding compared with parenteral, reduces septic complications: the results of a meta-analysis. Ann Surg 216: 172–183
48. Hadfield RJ, Sinclair DG, Houldsworth PE, Evans TW (1995) Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. Am J Respir Crit Care Med 152: 1545–1548
49. Schroeder D, Gillanders L, Mahr K, Hill GL (1991) Effects of immediate postoperative enteral nutrition on body composition, muscle function, and wound healing. JPEN J Parenter Enteral Nutr 15: 376–383
50. Bower RH, Cerra FB, Bershadsky B, Licari JJ, Hoyt DB, Jensen GL, Van Buren CT, Rothkopf MM, Daly JM, Adelsberg BR (1995) Early enteral administration of a formula (impact registered trademark) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. Crit Care Med 23: 436–449
51. Müller TF, Müller A, Bachem MG, Lange H (1995) Immediate metabolic effects of different nutritional regimens in critically ill medical patients. Intensive Care Med 21: 561–566
52. Wheeler A, Bernard GR (1999) Current concepts: treating patients with severe sepsis. N Engl J Med 340: 207–214
53. Cerra FB, McPherson JP, Konstantinides FN, Konstantinides NN, Teasley KM (1988) Enteral nutrition does not prevent multiple organ failure syndrome (MOFS) after sepsis. Surgery 104: 727–733
54. Steiner M, Burges HR, Freeman LS, Gray SJ (1968) Effect of starvation on the tissue composition of intestine in the rat. Am J Physiol 215: 75–77
55. Galanos AN, Pieper CF, Kussin PS, Winchell MT, Fulkerson WJ, Harrell FE Jr, Teno JM, Layde P, Connors AF Jr, Phillips RS, Wenger NS (1997) Relationship of body mass index to subsequent mortality among seriously ill hospitalized patients. Crit Care Med 25: 1962–1968
56. Heslin M, Latkany L, Leung D, Brooks AD, Hochwald SN, Pisters PW, Shike M, Brennan MF (1997) A prospective randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. Ann Surg 226: 567–580
57. Zaloga GP (1999) Early enteral nutritional support improves outcome: hypothesis or fact? Crit Care Med 27: 259–261
58. American College of Chest Physicians Consensus Statement. Applied nutrition in ICU patients (1997) Chest 111: 769–778
59. Pingleton SK, Hadzima SK (1983) Enteral alimentation and gastrointestinal bleeding in mechanically ventilated patients. Crit Care Med 11: 13–16
60. Frost P, Bihari D (1997) The route of nutritional support in the critically ill: physiological and economical considerations. Nutrition 13 [Suppl]:58S–63S
61. Orr ME, Ryder MA (1993) Vascular access devices: perspective on designs, complications and management. Nutr Clin Pract 8: 145–152
62. Richet H, Hubert B, Nitemberg G, Andremont A, Buu-Hoi A, Ourbak P, Galicier C, Veron M, Boisivon A, Bouvier AM (1990) Prospective multicenter study of vascular-catheter-related complications and risk factors for positive central-catheter cultures in intensive care unit patients. J Clin Microbiol 28: 2520–2525
63. Heyland DK, Cook DJ, Guyatt GH (1993) Enteral nutrition in the critically ill patient: a critical review of the evidence. Intensive Care Med 19: 435–442
64. Braga M, Gianotti L, Vignalli A, Cestari A, Bisagni P, Di Carlo V (1998) Artificial nutrition after major abdominal surgery: impact of route of administration and composition of the diet. Crit Care Med 26: 24–30
65. Moore FA, Moore EE, Kudsk KA, Brown RO, Bower RH, Koruda MJ, Baker CC, Barbul A (1994) Clinical benefit of an immune-enhancing diet for early postinjury feeding. J Trauma 37: 607–615
66. Cerra FB, Lehmann S, Konstantinides N, Dzik J, Fish J, Konstantinides F, Li-Cari JJ, Holman RT (1991) Improve in immune function in ICU patients by enteral nutrition supplemented with arginine, RNA and menhaden oil is independent of nitrogen balance. Nutrition 7: 193–199

67. Galbán C, Montejo JC, Mesejo A, Marco P, Celaya S, Sanchez-Segura J, Farre M, Bryg DJ (2000) An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. Crit Care Med 28: 643–648
68. Atkinson S, Sieffert E, Bihari D (1998) A prospective, randomized, double-blind, controlled clinical trial of enteral immunonutrition in the critically ill. Crit Care Med 26: 1164–1172
69. Gadek JE, DeMichele SJ, Karlstad MD, Pacht ER, Donahoe M, Albertson TE, Van Hoozen C, Wenneberg AK, Nelson JL, Noursalehi M (1999) Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid and antioxidants in patients with acute respiratory distress syndrome. Crit Care Med 27: 1409–1420
70. American Society of Parenteral and Enteral Nutrition Board of Directors (1993) Guidelines for the use of parenteral and enteral nutrition in adult and paediatric patients. JPEN J Parenter Enteral Nutr 17: 1SA–26SA
71. Klein S, Kinney J, Jeejeebhoy K, Alpers D, Hellerstein M, Murray M, Twomey P (1997) Nutrition support in clinical practice: review of published data and recommendations for future research directions. JPEN J Parenter Enteral Nutr 21: 133–156
72. Wojnar MM, Hawkins WG, Lang CH (1995) Nutritional support of the septic patient. Crit Care Clin 11: 717–733
73. Preiser JC, Berré J, Carpentier Y, Jolliet P, Pichard C, Van Gossum A, Vincent JL (1999) Management of nutrition in European intensive care units: results of a questionnaire. Intensive Care Med 25: 95–101
74. Mizock BA, Troglia S (1997) Nutritional support of the hospitalized patient. Dis a month 43: 351–426
75. Fisher RL, Pipkin GA, Wood JR (1995) Stress-related mucosal disease. Crit Care Clin 11: 323–345
76. Tryba M (1999) Research on stress ulcer prophylaxis: wrong questions, wrong answers? Crit Care Med 27: 16–17
77. Tryba M (1987) Risk of acute stress bleeding and nosocomial pneumonia in ventilated intensive care unit patients: sucralfate verus antacids. Am J Med 83: 117–124
78. Garvey BM, McCambley JA, Tuxen DV (1989) Effects of gastric alkalinization on bacterial colonization in critically ill patients. Crit Care Med 17: 211–216
79. Cook DJ, Fuller HD, Guyatt GH, Marshall JC, Leasa D, Hall R, Winton TL, Rutledge F, Todd TJ, Roy P (1994) Risk factors for gastrointestinal bleeding in critically ill patients. N Engl J Med 330 377–381
80. Layne EA, Mellow MH, Lipman TO (1981) Insensitivity of guaiac slide test for detection of blood in gastric juice. Ann Intern Med 94: 774–776
81. Schentag JJ (1980) False positive "hemoccult" reaction with cimetidine. N Engl J Med 303: 110
82. Schuster DP, Rowley H, Feinstein S, McGue MK, Zuckerman GR (1984) Prospective evaluation of the risk of upper gastrointestinal bleeding after admission to a medical intensive care unit. Am J Med 76: 623–629
83. Zandstra DF, Stoutenbeek CP (1994) 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 20: 335–340
84. Pinilla JC, Oleniuk FH, Reed D, Malik B, Laverty WH (1985) Does antacid prophylaxis prevent upper gastrointestinal bleeding in critically ill patients? Crit Care Med 13: 646–650
85. Peura DA, Johnson LF (1985) Cimetidine for prevention and treatment of gastroduodenal mucosal lesions in patients in an Intensive care unit. Ann Intern Med 103: 173–177
86. Groll A, Simon JB, Wigle RD, Taguchi K, Todd RJ, Depew WT (1988) Cimetidine prophylaxis for gastrointestinal bleeding in an intensive care unit. Gut 27: 135–140
87. Basso N, Bagarani M, Materia A, Fiorani S, Lunardi P, Speranza V (1981) Cimetidine and antacid prophylaxis of acute upper gastrointestinal bleeding in high risk patients. Am J Surg 141: 339–342
88. Ben-Menachem T, Fogel R, Patel RV, Touchette M, Zarowitz BJ, Hadzijahic N, Divine G, Verter J, Bresalier RS (1994) Prophylaxis for stress-related gastric hemorrhage in the medical intensive care unit: a randomized, controlled, single-blind study. Ann Intern Med 121: 568–575
89. Borrero E, Bank S, Margolis I, Schulman ND, Chardavoyne R (1985) Comparison of antacid and sucralfate in the prevention of gastrointestinal bleeding in patients who are critically ill. Am J Med 79: 62–64
90. Bresalier RS, Grendell JH, Cello JP, Meyer AA (1987) Sucralfate versus titrated antacid for the prevention of acute stress-related gastrointestinal hemorrhage in critically ill patients. Am J Med 83: 110–116
91. Cook D, Guyatt G, Marshall J, Leasa D, Fuller H, Hall R, Peters S, Rutledge F, Griffith L, McLellan A, Wood G, Kirby A (1998) A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. N Engl J Med 338: 791–797
92. Poleski MH, Spanier AH (1986) Cimetidine versus antacids in the prevention of stress erosions in critically ill patients. Am J Gastroenterol 81: 107–111
93. Stothert JC, Simonowitz DA, Dellinger EP, Farley M, Edwards WA, Blair AD, Cutler R, Carrico CJ (1980) Randomized prospective evaluation of cimetidine and antacid control of gastric pH in the critically ill. Ann Surg 192: 169–174
94. Skillman JJ, Bushnell LS, Goldman H, Silen W (1969) Respiratory failure, hypotension, sepsis and jaundice: a clinical syndrome associated with lethal hemorrhage from acute stress ulceration of the stomach. Am J Surg 117: 523–530
95. Hastings PR, Skillman JJ, Bushnell L, Sillen W (1978) Antacid titration in the prevention of acute gastrointestinal bleeding. N Engl J Med 298: 1041–1045
96. Lacroix J, Infante-Rivard C, Jenicek M, Gauthier M (1989) Prophylaxis of upper gastrointestinal bleeding in intensive care units: a meta-analysis. Crit Care Med 17: 862–886
97. Cook DJ, Reeve BK, Guyatt GH, Heyland DK, Griffith LE, Buckingham L, Tryba M (1996) Stress ulcer prophylaxis in critically ill patients: resolving discordant meta-analysis. JAMA 275: 308–314
98. MacDougall BRD, Bailey RJ, Williams R (1977) H-2 receptor antagonists and antacids in the prevention of acute gastrointestinal hemorrhage in fulminant hepatic failure. Lancet I:617–619
99. Metz CA, Livingston DH, Smith JS, Larson GM, Wilson TH (1993) Impact of multiple risk factors and ranitidine prophylaxis on the development of stress-related upper gastrointestinal bleeding: a prospective, multicenter, double-blind randomized trial. Crit Care Med 21: 1844–1849

100. Tryba M, Zevounou F, Torok M, Zenz M (1985) Prevention of acute stress bleeding with sucralfate, antacids or cimetidine. Am J Med 79 [Suppl 2C]:55–60
101. Luk GD, Summer WR, Messersmith JF (1982) Cimetidine and antacid in prophylaxis of acute gastrointestinal bleeding: a randomized, double blind, controlled study (abstract). Gastroenterology 82: 1121
102. Priebe HJ, Skillman JJ, Bushnell LS, Long PC, Silen W (1980) Antacid versus cimetidine in preventing acute gastrointestinal bleeding. N Engl J Med 302: 426–430
103. Cook DJ, Witt LG, Cook RJ, Guyatt GH (1991) Stress ulcer prophylaxis in the critically ill: a meta-analysis. Am J Med 91: 519–527
104. Bonten MJM, Gaillard CA, Van der Geest S, van Tiel FH, Beysens AJ, Smeets HG, Stobberingh EE (1995) The role of intragastric acidity and stress ulcus prophylaxis on colonization and infection in mechanically ventilated ICU patients. Am J Respir Crit Care Med 152: 1825–1834
105. Prod'hom G, Leuenberger P, Koerfer J, Blum A, Chiolero R, Schaller MD, Perret C, Spinnler O, Blondel J, Siegrist H (1994) Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine or sucralfate for stress ulcer: a randomized controlled trial. Ann Intern Med 120: 653–662
106. Hanisch EW, Encke A, Naujoks F, et al (1998) A randomized, double-blind trial for stress ulcer prophylaxis shows no evidence of increased pneumonia. Am J Surg 176: 453–457
107. Ben-Menachem T, McCarthy BD, Fogel R, Schiffman RM, Patel RV, Zarowitz BJ, Nerenz DR, Bresalier RS (1996) Prophylaxis for stress-related gastrointestinal hemorrhage: a cost effectiveness analysis. Crit Care Med 24: 338–345
108. Lam NP, Le PDT, Crawford SY (1999) National survey of stress ulcer prophylaxis. Crit Care Med 27: 98–103
109. American Thoracic Society (1995) Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy and preventive strategies. Am J Respir Crit Care Med 153: 1711–1725