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Immunological therapy in sepsis: currently available

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Introduction

Many therapies used in our daily practice are known to have significant effects on inflammation. These drugs influence the activation of the inflammatory network that occurs during severe sepsis and related syndromes as disseminated intravascular coagulation and acute respiratory distress syndrome (ARDS). Many of these compounds (Table 1) have already been used during experimental models of sepsis and/or human studies.

Methods

This contribution reviews those drugs that are available in the daily management of severe sepsis and septic shock. A computer-based review of the literature was undertaken using Medline from 1990 to September 1999 as the primary database. The subject heading keywords defined for each of the compounds listed in Table 1 were combined with the following general sepsis-related subject heading keywords: sepsis, severe sepsis, septic shock, and ARDS.

Anti-inflammatory agents

Should corticosteroids be used in the treatment of severe sepsis or septic shock at high doses (30 mg/kg) for a short course (one or 2 days)?

Answer: no, grade A.

Should corticosteroids be used during septic shock at low doses and for a prolonged period of time?

Answer: yes, grade C.

Recommendations

Corticosteroids should not be used in severe sepsis or septic shock at high doses (30 mg/kg) and for a short course (1–2 days). On the other hand, corticosteroids may be used during "refractory" septic shock but not during severe sepsis without shock or mild shock. It should then be used at low doses (100 mg hydrocortisone three times a day) for 5 days or more and then with subsequent tapering of the dose according to the hemodynamic status and the need for vasopressors.

Rationale

An extensive literature is available for corticosteroids. Steroids have been used for many years, and their efficacy is controversial. Numerous animal studies performed during experimental septic (endotoxic) shock or acute lung injuries showed a very significant reduction in both intensity of shock, acute respiratory failure and mortality [1, 2]. They have been used at very high doses (30 mg/kg per dose for a maximum of 24–48 h). The ability of these high doses of corticosteroids to reduce complement activation and to inhibit leukocyte aggregability and adherence was at that time a very logical rationale for their efficacy [3]. Very promising initial findings have been published regarding humans [12]. However, two well designed, prospective, multicenter, randomized, double-blind studies demonstrated very clearly their inability to decrease mortality [5, 8]. Some studies mention positive trends when looking at subgroups of infections due to Gram-negative rods [5, 8, 13].

Table 1 List of therapies currently available for eventually treating severe sepsis

Therapy	References
Anti-inflammatory agents	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38
Corticosteroids (high or low doses)	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 25a
Ibuprofen	27, 28, 29, 30, 31
Prostaglandin E_1	32, 33, 34, 35
Pentoxifylline	36, 37, 38
Oxygen scavengers	39, 40, 41, 42, 43, 44, 45, 46, 47
N-Acetylcysteine	39, 40, 41, 42, 43, 44, 45
Selenium	46, 47
Drugs modifying coagulation	48, 49, 50, 51, 52
Antithrombin III	48, 49, 50, 51, 52
Drugs enhancing host defenses	53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70
Immunoglobulins	54, 55, 56, 57, 58
Interferon-γ	59, 60, 61, 62, 63, 64
Granulocytes stimulating factors	65, 66, 67, 68, 69, 70
Immunonutrition	–[a]
Other drugs	71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85
Growth hormone	71
Antibiotics	72, 73, 74, 75, 76, 77
Including ketoconazole	73, 74
Including polymyxin B	72
Taurolidine	78
Fresh frozen plasma	79
Anesthetic sedative and analgesic agents	80
Catecholamines	81, 82, 83, 84, 85
Hemofiltration, plasma filtration, plasma exchange	86, 87, 88, 89, 90, 91

[a]See Pérez and Dellinger, "Other supportive therapies in sepsis"

Two recent meta-analyses [13, 14] reviewing the studies confirm that corticosteroids at the dose of 30 mg/kg (one or two doses) are ineffective [13] or even harmful [14]. The design and the results of the nine randomized studies are summarized in Tables 2 and 3. Similar negative results have been obtained during ARDS [15]. Pooling the results only from those patients with Gram-negative infections, as in the meta-analysis by Lefering et al. [13], yields a rate difference of –5.6 % [confidence interval (CI): –21.4 to 10.1) in favor of steroids, based on 413 patients. Those patients with Gram-positive infections (n = 306) had an overall effect of +1.8 % (CI: –15.8 to 18.6). Most persons stopped using steroids when these large trials were published.

Several studies performed over the years, however, have maintained interest in the use of corticosteroids. Mortality was reduced using steroids during severe typhoid fever [16], and neurological sequelae were reduced during meningitis [17]. Two large double-blind case control studies demonstrated that prolonged treatment (10–15 days) of relatively low doses of steroids (120–240 mg hydrocortisone) dramatically reduced mortality during severe *Pneumocystis carinii* pneumonia in AIDS patients [18, 19]. In addition, Meduri et al. [20] showed that the course of late, fibrotic ARDS was improved by steroid use which was confirmed in a recent randomized double-blind study showing a significant reduction in mortality [21]. Two small, randomized, double-blind studies of steroids in patients with severe and refractory septic shock recently demonstrated positive results [22, 23]. Corticosteroids were used at small doses (100 mg hydrocortisone three times per day in one [22] and 100 mg followed by a continuous infusion of 0.18 mg/kg per hour in the other [23], for longer periods of time than in past studies: 5 days in one [22] and 5–10 days in the other, with tapering of the doses according to hemodynamic status and need for vasopressors. Both studies showed a significant reversal of shock and organ failures and a trend in reduction in mortality. Additional studies are necessary, and a French multicenter randomized, controlled, double-blind study reported that low dose steroids decrease mortality in patients with septic shock [25 a].

Several factors may explain the recent positive effects of corticosteroids during sepsis [24]. These include the treatment of "relative" adrenal insufficiency [25] and the potentiation of adrenergic receptivity [26] in addition to the anti-inflammatory effect. The lower immunosuppressive doses and a more prolonged duration of therapy than in the initial studies could also explain discrepancies.

Table 2 Design of the nine randomized studies used in the meta-analysis (from Cronin et al. [14]) (*DB* double blind, *M* methylprednisolone, *B* betamethasone, *D* dexamethasone, *H* hydrocortisone)

Reference	*n*	Type of study	Product	Dose	Duration	Endpoints
Cooperative Study Group [6]	194	Open	H	300 mg then 50 mg/d	6 d	Mortality, complications
Klastersky et al. [10]	85	Open	B	1 mg/kg	3 d	Mortality (20 d), complications
Schumer et al. [12]	172	DB	M	30 mg/kg	1 dose or 2	Mortality (28 d), complications
Thompson et al. [11]	60	DB	M	30 mg/kg	Max. 6 doses in 24 h	Mortality, complications
Lucas and Ledgerwood [9]	48	Open	D	2 mg/kg	2 d	Mortality (14 d), complications
Sprung et al. [4]	59	Open	M	30 mg/kg	1 dose (or 2)	Hospital mortality, complications
Bone et al. [5]	381	DB	M	30 mg/kg	1 d	Mortality (14 d), complications
Veteran Administration [8]	223	DB	M	30 mg/kg	9 d	Mortality (14 d), complications
Luce et al. [7]	75	DB	M	30 mg/kg×4	1 d	Hospital mortality, ARDS complications

Table 3 Results of the nine randomized studies used in the meta-analysis (from Cronin et al. [14])

	n	Risk ratio	95% CI
Cooperative study group [6]	194	1.72	1.23–2.41
Klastersky et al. [10]	85	0.97	0.65–1.45
Schumer et al. [12]	172	0.30	0.13–0.72
Thompson et al. [11]	60	1.01	0.77–1.31
Lucas et al. [9]	48	1.09	0.36–3.27
Sprung et al. [4]	59	1.11	0.74–1.67
Bone et al. [5]	381	1.35	0.98–1.84
Veteran Administration [8]	223	0.95	0.57–1.58
Luce et al. [7]	75	1.07	0.72–1.60

Should ibuprofen be used in the treatment of severe sepsis and septic shock?

Answer: no, grade B.

Recommendations

Ibuprofen should not be used during severe sepsis or septic shock. Additional studies are needed to determine whether some patients, for example, those with hypothermia, could benefit from the drug.

Rationale

Ibuprofen is a powerful anti-inflammatory agent, acting on the prostaglandin metabolism as a cyclo-oxygenase inhibitor. It has been used with controversial effects in animals during both experimental sepsis and ARDS [27, 28]. Two small randomized, double-blind studies in patients showed some hemodynamic effect and a normalization of pH without any significant effect upon mortality [29, 30]. Mortality was decreased significantly in a post hoc analysis of hypothermic patients [30]. A large multicenter randomized, controlled, double blind study, however, failed to demonstrate any effect upon mortality, reversal of shock or acute respiratory failure [31]. Ibuprofen was able to reduce the levels of prostacyclin and thromboxane and to decrease fever, tachycardia and oxygen consumption [31]. The drug was not associated with adverse affects.

Should prostaglandins be used in the treatment of ARDS due to severe infections and sepsis?

Answer: no, grade B.

Recommendations

Prostaglandins, in particular prostaglandin E_1 or liposomal prostaglandin E_1 should not be used during ARDS due to sepsis. There are no specific data allowing recommendations in severe sepsis.

Rationale

Several prostaglandins which have both an anti-inflammatory and a vasoactive effect have been studied including prostaglandin I_2 and particularly prostaglandin E_1 [32, 33, 34, 35] during ARDS. The vast majority of these patients had ARDS due to severe infections or sepsis. An early, small, randomized study showed promising results [32]. However, a large multicenter, randomized, controlled, double blind study failed to show any difference in survival [33]. An increase in oxygen delivery and oxygen consumption was noted in treated patients who survived [34]. A recent, multicenter randomized, controlled, double-blind study with liposomal prostaglandin E_1 (TLC C-53) showed that indices of oxygenation of treated ARDS patients were improved compared with controls, but without any effect upon duration of mechanical ventilation or 28 days mortality [35]. Again, most ARDS was due to sepsis in these two large studies. No data are really available concerning an overall group of patients with severe sepsis.

Should pentoxifylline be used in the treatment of severe sepsis in (a) adults, (b) infants?

Answer: (a) no, grade B; (b) no, grade C.

Recommendations

Pentoxifylline should not be used in adults with severe sepsis unless new studies show a significant effect. The positive effect of a small study in infants should be confirmed before clinical use.

Rationale

Pentoxifylline, which has a powerful anti-inflammatory effect including a strong inhibition of tumor necrosis factor secretion, has been used successfully in many animal studies with the prevention of the transition from a hyperdynamic to hypodynamic state, although no effect upon mortality has been shown [36]. Human studies are more scarce. A multicenter, randomized, controlled, double-blind study during sepsis showed an increase in PaO_2/FIO_2 ratio but no effect upon cytokines levels or mortality [37]. A recent double-blind study performed in premature infants with sepsis showed a decrease in cytokines levels and a significant decrease in mortality (1/40 vs. 6/38 $p = 0.046$) [38]. However, the size of this study was rather small, and additional large studies are mandatory.

Oxygen scavengers

Several oxygen scavengers are currently available, including *N*-acetylcysteine (NAC), vitamin E, vitamin C, and selenium. Vitamins E and C have been only poorly studied in humans, and we focus on *N*-acetylcysteine and selenium.

Should *N*-acetylcysteine be used in the treatment of severe sepsis?

Answer: no, grade C.

Recommendations

NAC should not be used in severe sepsis until new data are available, focusing in particular on very early therapy.

Rationale

During acute lung injury an improvement in oxygenation and reduction in the required length of mechanical ventilation was found in patients treated with NAC compared to controls [39]. However, several randomized studies have shown no difference in mortality, gas exchange, and development of respiratory failure in patients treated with NAC [39, 40]. Several studies have also been performed during severe sepsis, with heterogeneous results [41, 42, 43, 44]. Depressed cardiac performance has been described in septic patients treated with NAC [42]. A very recent multicenter, randomized, controlled, double-blind study showed that a prolonged infusion of NAC is unable to prevent multiple organ failure in consecutively admitted critically ill patients [43]. In this study treatment used more than 24 h after the initial insult worsened the prognosis compared to controls. Better results were obtained when the drug was use before the insult, as during cardiac surgery [44]. These results suggest that this compound could be helpful when started before (or perhaps shortly after) the insult, but possibly harmful when started too late. Combinations of several antioxidants have also been published, but data are too limited to allow recommendations [45].

Should selenium be used in the treatment of severe sepsis?

Answer: no, grade C.

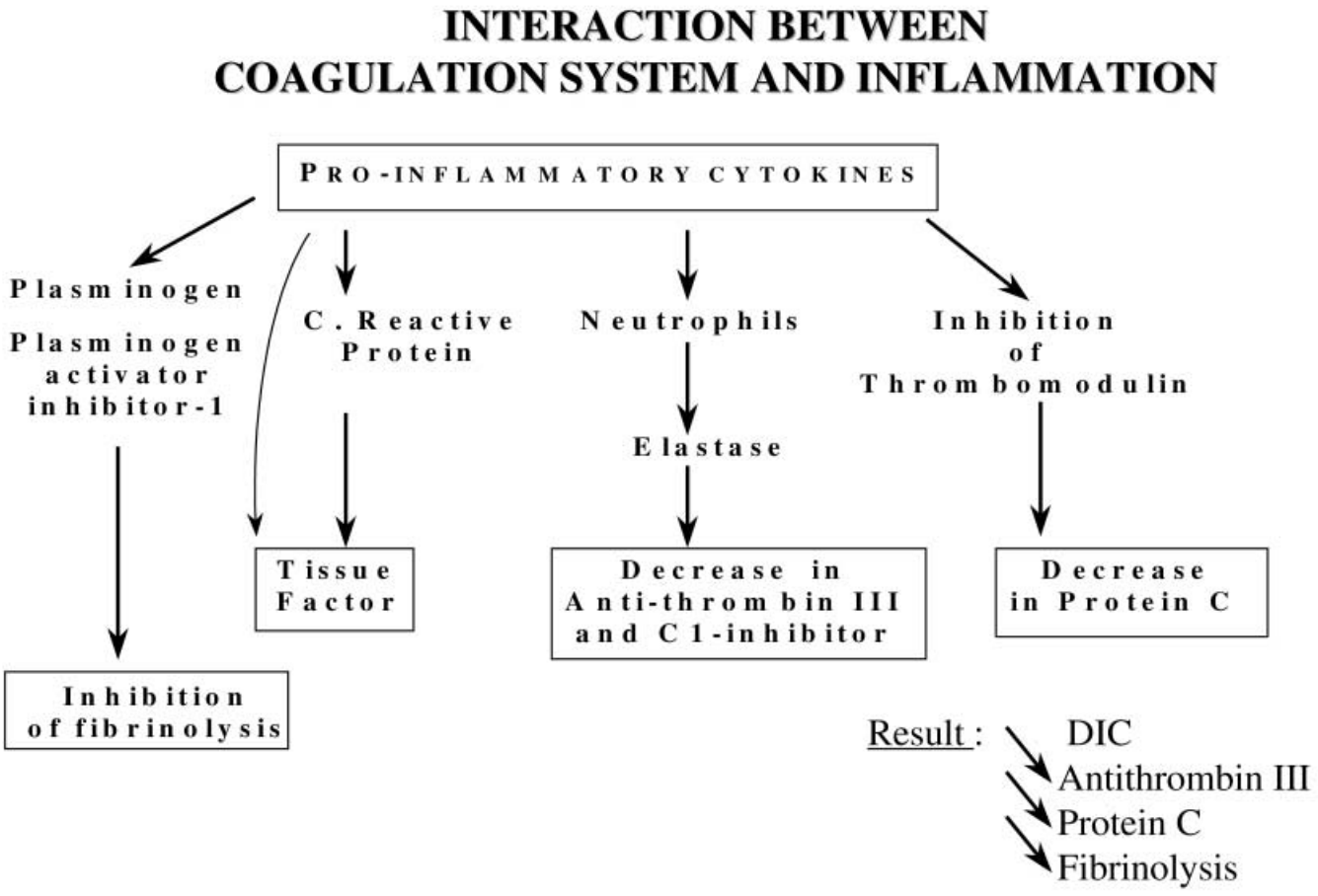

Fig. 1 Effect of proinflammatory cytokines. Upon coagulation cascade during sepsis leading to an activation of tissue factor, a depletion in protein C (via a decrease in thrombomodulin levels) antithrombin III and C1 inhibitor, and a decrease in fibrinolysis (via the effect of plasminogen activator inhibitor 1)

Recommendations

Selenium should not be used for severe sepsis. Additional studies are warranted to confirm initial positive data.

Rationale

A profound depletion in selenium levels has been demonstrated in many severe septic patients [46]. Mortality and morbidity are far higher in patients with a very low selenium level [46]. A recent prospective, randomized, but nonblinded study performed in septic patients showed that selenium replacement is able to reduce severity indexes at day 3 and reduce the need for hemodialysis but has no significant effect upon mortality (52% in controls and 33, 5% in treated patients, $p = 0.13$) [47]. Additional large studies are needed to confirm initial promising results.

Drugs modifying coagulation

There are complex interactions between the inflammation and coagulation systems (Fig. 1). Proinflammatory cytokines activate coagulation cascades, in particular via an effect upon tissue factor which is a key player in the coagulation cascade. They can also reduce fibrinolysis and profoundly reduce the levels of protein C and of antithrombin III which are important anticoagulant agents. Antithrombin III inhibits several coagulation factors of the extrinsic pathway such as factors IXa, XIa, XIIa in addition to factors Xa, IIa, and plasmin. Activated protein C inhibits factors Va, Vlla, and plasminogen activator inhibitor 1. The overall effect during sepsis is a marked procoagulant balance. Conversely, coagulation products can activate the inflammation network which creates numerous amplification loops. For example, thrombin can induce an up-regulation of P- and E-selectin, and contact factor activation can induce the production of bradykinin, worsening hypotension and tissue hypoperfusion. In humans studies, both anti-

thrombin III and protein C levels are sharply decreased [48], and mortality of septic patients is inversely correlated with the levels of those two products. This makes the rationale for studying those types of compounds, such as antithrombin III, protein C, and tissue factor protein inhibitor very strong. Only antithrombin III is currently available.

Should antithrombin III be used in the treatment of severe sepsis?

Answer: no, grade B.

Recommendations

Antithrombin III should not be used during severe sepsis. Countries which allow the free use of this drug in this setting should reconsider their position.

Rationale

Antithrombin III is a drug which is widely used for septic patients in several countries. Three randomized, small, double-blind studies were published [49, 50, 51]. Duration of disseminated intravascular coagulation was reduced [49] as well as the number of organ failures [51], but mortality was not different although a positive trend was clearly noted. A meta-analysis was also performed [51] showing a 22.9% reduction in mortality but which did not reach statistical significance. Unfortunately a large multicenter, prospective, double-blind study has recently been completed which showed no significant improvement in survival [52]. The complete data have not yet been published. Other drugs such as activated protein C and tissue factor inhibitors are not currently available and are discussed elsewhere (see Arndt and Abraham, "Immunological therapy of sepsis: experimental therapies").

Drugs enhancing host defenses

After the initial activation of the proinflammatory network, a profound immunodepression can occur in septic patients [53]. This could influence outcome increasing the risk of nosocomial infections. Several strategies have been used to increase host defenses, including polyvalent immunoglobulins, interferon-γ, stimulating factors for granulocytes [including granulocyte colony stimulating factor (G-CSF)], and immunonutrition. The latter is discussed elsewhere (see Pérez and Dellinger, "Other supportive therapy in sepsis").

Should intravenous immunoglobulins be used in the treatment of severe sepsis in (a) adults or (b) neonates?

Answer: (a) no, grade C; (b) no, grade C.

Recommendations

Immunoglobulins should not be used either in adult patients or in neonates with sepsis, unless additional large studies confirm some positive data in small-sized meta-analyses. Countries which allow a wide use of these compounds should reconsider their position and encourage these studies.

Rationale

Intravenous immunoglobulins (IVIG) are widely used in both infants and adults in the treatment of severe sepsis, at least in certain countries. Reports which support their empirical use, however, are still rather weak. The rationale is to restore immunoglobulins levels, which may be depressed in sepsis, and to provide patients with specific antibodies against micro-organisms. No individual well designed clinical study has been performed in adults with severe sepsis. A recent study was performed in patients with streptococcal toxic shock syndrome [54]. This was a comparative nonblinded study performed in 21 patients which demonstrated a significantly reduced mortality (67% vs. 34%, $p = 0.02$). Both Acute Physiology and Chronic Health Evaluation II scores and IVIG were prognostic factors in the multivariate analysis. The odds ratio associated with IVIG was 8.1 (95% CI: 1.6–45). A recent meta-analysis by the Cochrane group [55] looking at 23 studies (some of them unpublished) on immunoglobulins, antiendotoxins, and anticytokines, extracted from the small size studies already published, evaluated a population of 413 patients receiving polyclonal immunoglobulins. Mortality was significantly reduced (relative risk: 0.6; 95% CI: 0.47–0.76). Results were even more positive when only sepsis related deaths were considered. A large, well designed, multicenter, randomized, double-blind study is, however, warranted before making firm conclusions. Two prophylactic studies have been published recently [56, 57]. A study performed in cardiac surgery patients showed no difference in the occurrence of sepsis between polyvalent IVIG and IgM-enriched immunoglobulin [56]. A prospective comparative study showed that IVIG and not placebo is able to prevent nosocomial infections after major surgery [57]. Such prophylactic studies are needed in this field in nonsurgical critically ill patients.

In neonatal sepsis, a recent meta-analysis of 110 newborns in three studies showed that IVIG is able to re-

duce mortality significantly (odds ratio: 0.173; 95 % CI: 0.031–0.735; $p = 0.007$) [58]. However, the size of the overall population was very small, and large studies are urgently warranted. In the same meta-analysis the effect of IVIG in the prevention of sepsis in 4933 evaluable newborns was significant ($p = 0.0193$, two-tailed), although heterogeneity of the studies precluded estimation of an overall odds ratio.

Interferon-γ

Interferon-γ has been used successfully in animals models of Gram-negative sepsis [59, 60]. Few data are available in human sepsis. The drug has been used with positive results to prevent infection during chronic granulomatous disease [61] and trauma [62, 63]. The drug, however, was unable to prevent infections in burn patients [64]. Data are insufficient for therapy of severe sepsis to allow recommendations.

Should granulocyte colony stimulating factor be used in the treatment of severe infections?

Answer: no, grade C.

Recommendations

G-CSF should not be used in nonneutropenic patients with severe sepsis.

Rationale

G-CSF is very efficient and reduces mortality in animal models of abdominal sepsis [65, 66]. During pneumonia models in rats the drug has been shown to exert different effects according to the micro-organisms involved [67]. Preliminary studies have been performed in community or hospital acquired pneumonia with controversial results [68, 69]. In patients with head trauma and receiving mechanical ventilation G-CSF prophylaxis did not improve outcome nor lower the risk of nosocomial pneumonia [70].

Immunonutrition

See Pérez and Dellinger, "Other supportive therapies in sepsis."

Other Drugs

Should growth hormone be used in the treatment of severe sepsis?

Answer: no, grade A.

Recommendations

Growth hormone should not be used in patients with sepsis because it increases mortality.

Rationale

The administration of growth hormone could in theory attenuate the catabolic response to injury, surgery or sepsis. Two prospective double-blind studies with more than 200 patients each were recently reported in critically ill patients with cardiac or abdominal surgery, multiple trauma or acute respiratory failure [71]. Mortality was increased significantly in treated patients. The relative risk in these two pooled studies was 1.9 (95 % CI: 1.3–2.9). Length of stay and duration of mechanical ventilation were longer in treated survivors than in controls.

Antimicrobial compounds

Polymixin B. Polymixin B is able to neutralize endotoxin via strong antilipid A activity [72]. Since it is very toxic, it is difficult to use intravenously in humans, although some derivates are less toxic. Extracorporeal techniques, in which polymyxin is coated on membranes, are under investigation.

Ketoconazole. Ketaconazole, one of the new imidazoles, has a strong effect upon thromboxane synthase inhibition and has been shown to prevent ARDS in septic patients in a small double-blind randomized study [73]. A recent study performed in 234 patients, however, failed to demonstrate any effect upon mortality and duration of mechanical ventilation in ARDS patients [74]. No data are available in patients with sepsis.

Other antibiotics

Some antibiotics have anti-inflammatory effects, in particular in decreasing cytokine release. Effects have been shown for vancomycin [75] trovafloxacin [76] and ciprofloxacin [77].

Taurolidine

Taurolidine is an anti-infective agent (nonantibiotic), used either locally, or intravenously, which has some antibacterial effect associated with an antiendotoxin effect. A randomized placebo-controlled study failed to demonstrate any effect on outcome in sepsis [78].

Other drugs currently used

Many other drugs that we use daily could have important effects upon inflammation, including heparin, fresh frozen plasma [79], and anesthetic, sedative, and analgesic agents [80]. A recent review [80] describes the potential effects of these agents upon immunomodulation.

Catecholamines and inflammation. It is well known that inotropic agents such as catecholamines have a significant impact upon inflammation [81]. Epinephrine inhibits tumor necrosis factor and potentiates interleukin-10 leading to a significant anti-inflammatory effect [82], via an effect upon macrophages [83]. Dopamine increases interleukin-6 release but decreases tumor necrosis factor [84]. Recent data support the concept that the anti-inflammatory effect of catecholamines explains the possible beneficial effects of supranormal oxygen delivery in critically ill surgical patients [85]. These data do not enable clinicians to take into account the effect of catecholamines upon inflammation in deciding which is the best to use.

Hemofiltration and plasma filtration

Should hemofiltration be used in the treatment of patients with severe sepsis, without renal indications?

Answer: no, grade C.

Recommendations

Hemofiltration should not be used in patients with sepsis without renal indications unless ongoing studies provide positive results.

Rationale

Hemofiltration has been shown to decrease cytokines levels significantly, although temporarily during severe sepsis in humans. The technique is widely used in Europe and many authors have strong opinions [86] regarding its use, although the data are weak. A randomized, still unpublished study found no effect upon mortality [87]. Another randomized controlled study [88] reported a 15% (nonsignificant) increase in survival for filtrated patients. Favorable results have been described for cardiac surgery patients [89]. Large multicenter studies are currently under way.

Plasma filtration induced a significant attenuation of acute-phase response in a randomized, prospective study recently performed in 22 adults with sepsis [90]. However, no difference in mortality and only a trend toward fewer organ failures were noted. Plasma exchange has also been used in severe meningococcemia in children [91] with varying results.

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