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REVIEW ARTICLE

Advances in sepsis diagnosis and treatment

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Objective: To present a critical and updated review about sepsis, focusing especially on diagnosis and treatment.

Sources of data: Literature review of Medline, including review articles, clinical trials and original research.

Summary of the findings: The International Sepsis Definitions Conference amplified the list of possible clinical and laboratory signs of sepsis, which may allow for more efficacious suspicion and management. In terms of laboratory evaluation, in addition to the research for infectious agents, many inflammatory response markers, such as inflammatory cytokines and procalcitonin, have been identified. However, they lack sensitivity and specificity for safe diagnosis. In terms of treatment, early intervention to prevent hemodynamic disturbances is still essential for a positive outcome, together with the appropriate use of antimicrobials. The value of treatments to remove toxins and to increase the innate immune response has not yet been established. The use of isolated inflammatory response blockers, at any stage of sepsis, does not decrease mortality. The use of corticosteroid makes a comeback with encouraging results, even in patients without sepsis-related adrenal insufficiency. A large study on activated protein C (drotrecogin-α) reports a 6% decrease in mortality in a selected sample, suggesting the possibility of a better prognosis for sepsis patients.

Conclusions: In comparison to the advances of the past few years, little has been achieved in terms of decreasing sepsis-related mortality due to the complexity of the pathogen-host relationships. The individual regulation of host reactions did not have the expected effects. The benefits of some known strategies were confirmed. Other types of treatment, such as corticosteroids and activated protein C therapies, are emerging as promising alternatives. Research indicates that the combination of immune modulator therapies is probably the best choice to improve outcomes in sepsis.

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"Our arsenals for fighting off bacteria are so powerful, and involve so many different defense mechanisms, that we are more in danger from them than from the invaders.

We live in the midst of explosive devices; we are mined."

Lewis Thomas, 1972

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Introduction

Sepsis is a complex syndrome caused by an uncontrolled systemic inflammatory response, of infectious origin, characterized by multiple manifestations and which can result in dysfunction or failure of one or more organs and even death.

During the last decade innumerable advances were made in understanding the pathophysiology of this syndrome, by means of multicenter studies, which resulted in the suggestion of certain diagnostic markers and in the potential

benefit of innumerable treatments alternatives.[1-3] In recent years researchers in recent years have persistently pursued the achievement both of early diagnosis and of a change or arrest of its clinical course. However, the poor clinical evolution and the continued high mortality among sepsis patients do are not signs of an early or successful outcome to the hunt for solutions to this condition.

Since the 1991 Consensus, new definitions and criteria for the diagnosis of sepsis, although lacking specificity, particularly for pediatric patients,[4] have enabled researchers to speak the same language and compare the results of their experiments. In 2001, the International Sepsis Definitions Conference, congregating a larger number of researchers and experts from all over the world, opted not to modify the existing definitions and to increase the list of signs and symptoms of sepsis (Table 1), thus valuing the clinical experience of intensive care professionals.[5]

The use of the term sepsis is not restricted to a systemic inflammatory syndrome secondary to bacterial infection, but to this syndrome resulting from any microorganism and/or its products (toxins). The term sepsis is applicable only when the systemic response is clinically relevant, which can manifest in a variety of situations of increasing complexity: (a) severe sepsis, understood as sepsis associated with organ failure, hypoperfusion (which includes, but is not limited to lactic acidosis, oliguria or an acutely altered state of consciousness) and hypotension; (b) septic shock, understood as sepsis associated with hypoperfusion alterations, but with persistent hypotension even after suitable volumetric resuscitation, and (c) multiple organ failure syndrome (MOFS), which may represent the final stage of the severe systemic inflammatory reponse.[5-7] However, the limits which separate sepsis from severe sepsis and this from septic shock are not easily detected in clinical at ICUs, or even from a conceptual point of view.[8,9] The last conference on sepsis proposed the development of a system of stages for sepsis which would better classify the syndrome based on pre-disposing factors and on pre-morbid conditions, in the nature of the subjacent infection, in the characteristics of the response of the host and the extension of resultant organ dysfunction (PIRO - Predisposition Infection Response Organ Dysfunction).

Table 1 - Diagnostic criteria for sepsis

Infection, documented or suspected, and some of the following:

– **General variables**
Fever (core temperature > 38.3 °C)
Hypothermia (core temperature < 36 ºC)
Heart rate > 90 min^{-1} or > 2 SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (> 20 ml/kg over 24 hrs)
Hyperglycemia (plasma glucose > 120 mg/dl or 7.7 mmol/l) in the absence of diabetes

– **Inflammatory variables**
Leukocytosis (WBC count > 12,000/mm^3)
Leukopenia (WBC count < 4,000/mm^3)
Normal WBC count with > 10% immature forms
Plasma C-reactive protein > 2 SD above the normal value
Plasma procalcitonin > 2 SD above the normal value

– **Hemodynamic variables**
Arterial hypotension (SBP < 90 mm Hg, MAP < 70, or an SBP decrease > 40 mm Hg in adults or < 2 SD below normal for age)
SvO_2 > 70%
Cardiac index > 3.5 l/min-1/M^{-23}

– **Organ dysfunction variables**
Arterial hypoxemia (PaO_2/FIO_2 < 300)
Acute oliguria (urine output < 0.5 ml/kg^{-1}/hr^{-1} or 45 mmol/l for at least 2 hrs)
Creatinine increase > 0.5 mg/dl
Coagulation abnormalities (INR > 1.5 or aPTT > 60 secs)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100,000/mm^3)
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dl or 70 mmol/l)

– **Tissue perfusion variables**
Hyperlactatemia (> 1 mmol/l)
Decreased capillary refill or mottling

Modified from Levy et al. 2001 International Sepsis Definitions Conference. SD - standard deviation; WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial blood pressure; SvO_2, mixed venous oxygen saturation; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

Epidemiology

Sepsis is a heavy burden on health services all over the world, both from economic and social points of view. According to an epidemiological study of the USA, over the last 20 years, the incidence of sepsis increased from 82.7 to 240.4/100 thousand inhabitants, as did the deaths related to it, although the general mortality rate among patients with sepsis was reduced over the period.[10] A study by Watson et al., based on pediatric hospital discharge records in the USA in 1995, revealed a prevalence of 0.56 child cases of severe sepsis per 1,000 habitants/year.[11] Angus et al., across 847 federal hospitals in the USA, in 1995, found three cases of severe sepsis for each group of 1,000 inhabitants and 2.26 cases for each group of 100 hospital discharges, 68% of whom had received some sort of intensive or intermediate care. Global mortality was around 28%, but varied according to age group: 10% of children and 38% elderly, 85 years or older.[12] According to Brun-Buisson et al., based on French adult ICUs, mortality at 28 days after discharge was 56% for severe sepsis and 60% for severe sepsis with a negative culture.[13] In the study carried out by Angus et al., the costs caused by sepsis were highest among infants, non-survivors, patients in ICU, surgical patients and in those with failure of more than one organ.[12]

The increase in morbidity and mortality incidence rates related to sepsis of recent decades is directly related to the medical advances achieved during this period, where, more and more, seriously ill patients and those in more advanced stages are treated. At least 50 of the cases reported on by Watson et al. Had a subjacent disease, while 23% were low birth weight newborns.[11] Another relevant aspect which should be considered is that of secondary sepsis among critically ill patients hospitalized for other reasons, whether because of immunological compromise or because of medical conduct and procedures carried out during their ICUs and hospital stay.[14]

The rates of sepsis reported in published literature can vary according to local characteristics. In the USA and Europe, sepsis is responsible for 2-11% of ICU admissions.[15] A retrospective analysis by Jacobs et al., of more than 2000 Pediatric ICU admissions, identified 42.5% of patients with and infectious disease, of whom 63% had septic shock.[16] Proulx et al., evaluating 1058 admissions to a PICU at a Canadian teaching hospital, identified 82% Systemic Inflammatory Response Syndrome (SIRS), of which 23% had infectious etiology (sepsis), 2% of which had septic shock.[9]

Diagnosis

The diagnosis of sepsis is the first of the challenges which confront the clinician or intensive care specialist, especially because its identification, when not sufficiently early to allow intervention, may result in shock, organ failure or even patient death. Early sepsis diagnosis continues to be one of the most difficult of tasks, whether because the first clinical manifestations may pass unnoticed or because they can be confused with those of other, non infectious, processes. Furthermore, the indirect laboratory indications (hemagram, coagulation study, glycemia, etc), usually employed to reach a diagnosis of sepsis, individually have little sensitivity and less specificity. Similarly, the results of bacteriological examinations collected on the occasion of first suspicion are not immediately available to guide specific therapy.

During the last decade, innumerable markers have been suggested for early sepsis diagnosis, among which are serum assay of certain cytokines - interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8) e interleukin-10 (IL-10), tumor necrosis factor (TNF), of their respective soluble receptors (TNF receptor), acute phase proteins (C-reactive protein) and procalcitonin.[17]

Clinical

The criteria of the 1991 Consensus which defined SIRS secondary to infection (sepsis), in addition to being inappropriate for pediatric patients, were unspecific even for adult patients. Observation and care of patients in Pediatric and Neonatal ICUs has shown that the signs and symptoms of sepsis are highly variable, depending on patient age group, and are not restricted to simply changes to certain physiological variables. Thus, the younger the child, the less specific the symptoms of sepsis. No clinical sign is sensitive or specific enough to indicate severe infection, especially in seriously ill patients.[14]

A recent International Conference on the Definition of Sepsis, while maintaining the definitions proposed by the previous consensus, extended the list of possible clinical and laboratory signs of sepsis, considering innumerable indicators of severe infection in the child (Table 1). The researchers and experts considered bedside diagnosis of sepsis to have priority over criteria for inclusion in clinical studies.[5]

Therefore, for the clinician or intensive care specialist, the diagnosis of sepsis is based on a high level of suspicion, which demands a minutely detailed collection of information on present status and medical history of the patient, a good clinical evaluation, certain laboratory tests, in addition to rigorous clinical monitoring of the patient. Faced with a suspicion of severe infection, the possibility of other, non-infectious, systemic inflammatory conditions should be ruled out.

Laboratory

Laboratory, or complementary, evaluation is capable of revealing two distinct aspects of sepsis. The first is related to the search for the aggressive agent, by means of microbiological tracking of the patient; the second relates to the identification of alterations to metabolism or homeostasis, indicative of systemic compromise or of specific organ involvement.

Microbiological evaluation includes direct tests and cultures of blood (two or more), of urine, of cerebrospinal fluid, of feces, of secretions, of small intestine aspirate, of exudates, and of petechiae and suffusions (when meningococcemia is suspected), preferably before using antimicrobial treatments (AMs). Cerebrospinal fluid must always be obtained, especially for newborns and young infants, being careful to obtain it safely, i.e. without risk to the patient.

In the case of hospitalized patients, the collection of material for culture should include all devices that breach the host's protective barriers, i.e. venous or arterial catheters (blood from the catheters), vesicle probes, tracheal tube or tracheostoma (tracheal aspirate), and stitches or scars from recent surgery.

Despite the great effort made to isolate microorganisms, on average, blood cultures are positive in 34% of "septic" patients, varying from 9 to 64%.[18] How many of these episodes are sepsis without bacteremia or failures of microbiological cultivation and identification methods, or even non-infectious SIRS, remains unknown.

On suspicion of sepsis with a patient who has had a long duration ICU stay, an investigation for systemic

infection by fungus is mandatory. Currently, fungi, and especially species of Candida, are responsible for around 5% of sepses.[18] The presence of additional risk factors increase the chance of fungal infection, such as the use of multiple AM treatments, broad spectrum AMs, parenteral nutrition, prolonged presence of central catheter and colonization of the digestive tract by Candida.

The laboratory evaluation to identify systemic compromise includes from the search for inflammatory response indicators in peripheral blood (endogenous mediators, acute phase indicators) to the testing for indicators of organic and metabolic disturbances in order to treat and support them. Indicators of the presence of systemic inflammatory response, in the majority, lack sensitivity and specificity for sepsis diagnosis, but can be of value for prognosis and monitoring therapeutic response. Increases in serum lactate, serum cytokines, granulocyte colony stimulating factor and of plasma nitric oxide (by means of nitrite/nitrate plasma levels) can be early indicators of SIRS, although the majority of them are not available quickly. Procalcitonin, which is liberated into circulation together with cytokines, and has a longer half-life, may have value for early diagnosis of neonatal sepsis.[14] In adults, procalcitonin has been referred to as an indicator of sepsis in patients with SRIS,[19] and as a prognostic instrument with septic patients.[20] Despite its great potential, at the moment procalcitonin cannot yet be defined as a marker for sepsis in patients with SIRS, and is perhaps more useful for excluding the diagnosis.[21]

Treatment

The systemic inflammatory response in sepsis, due to reasons that have not yet been established, may be restricted to an self-limiting phenomenon or can proceed through stages of greater severity, such as severe sepsis, septic shock and dysfunction or failure of one or more organs. Despite the large number of investigations and reports on SIRS, sepsis and related syndromes during recent years, and the undeniable improvement in understanding their respective pathogeneses, the initial approach to sepsis continues to be predominantly one of support. On suspicion of SIRS, if no other significant, non-infectious event is detected, conduct should be directed at sepsis; in addition to life support measures when indicated, other steps should be taken depending upon the severity and presentation of the respective syndrome.

Early goal-directed therapy

The limits separating sepsis from severe sepsis, and this from septic shock or multiple organ failure are not easily detected in clinical practice.[8,9] During the course of the evolution of the inflammatory response resuscitation phenomena such as hypovolemia, peripheral vasodilation, myocardial depression, increased endothelial permeability and hypermetabolism occur. Thus, in general, the intensive care specialist is led to correct pre-load, post-load and cardiac contractility to attend to the oxygen tissue supply/demand ratio, to maintain adequate cellular perfusion and prevent organ dysfunction.[22]

Similarly, just as the first hour is of extreme importance in the evaluation and primary care of the trauma victim, with sepsis too, evolution to a more critical condition in general occurs outside of the ICU. It is during the lapse of hours which precedes the patient's admission to the ICU that early recognition of poor evolution of sepsis and a more aggressive treatment can produce benefits necessary to change the outcome.[23]

According to Rivers et al.,[24] early hemodynamic assessment with a basis in a physical examination, on vital signs, on central venous pressure and urinary output is not sufficient to detect persistent global tissue hypoxia. They recommend a more definitive resuscitation strategy, with therapy oriented by goals, which include manipulation of pre-load (CVP between 8 and 12 mmHg), post-load (MAP $\geq$ 65 mmHg and $\leq$ 90 mmHg) and cardiac contractility (oxygen saturation of mixed venous blood [SvO_2] $\geq$ 70%), to achieve equilibrium between supply and demand for systemic oxygen. The therapy proposed, which should occur during the first 6 to 8 hours after identification of the septic patient, including vigorous volumetric resuscitation every 30 minutes, until a CVP between 8 and 12 mmHg is achieved; use of vasopressors if MAP $\leq$ 65 mmHg, attempting always to maintain it above this level, or use of vasodilators if MAP $\geq$ 90 mmHg, attempting to maintain it below this limit; and, if SvO_2 $\leq$ 70%, transfusion of erythrocyte concentrate to achieve hematocrit at a minimum of 30%. After optimizing CVP, MAP and hematocrit, if SvO_2 remains $\leq$ 70%, use continuous dobutamine in increasing doses until SvO_2 $\geq$ 70% or until dobutamine has reached a limit of 20 µg/kg/min. The parameters for confirmation of the objective proposed include the normalization of SvO_2, arterial lactate concentration, base cardiac output and pH. This strategy of early sepsis treatment directed by objectives, when compared with a standard strategy resulted in fewer organic dysfunctions and lower mortality.[1,22,24]

While there are not yet any comparative studies available that use objective oriented therapy with pediatric patients, some of the observations made by Rivers et al. probably do not apply to children. In childhood septic shock there are always considerable volume deficits, irrespective of invasive monitoring, the infusion of large volumes of crystalloid solutions during the first hours of care is mandatory and is associated with a reduced mortality rate.[23] Even with a volumetric deficit of 25 to 30% of the volemia, a child's MAP remains stable for a longer period at the cost of increased systemic vascular resistance. In this manner, MAP is not a good sign for

indicating volumetric replacement in a child with shock. Additionally, the use of dopamine is preferred for inotropic treatment of children in place of dobutamine.[23]

Treatment of the aggressive agent

Antimicrobial (AMs) are the most specific and accessible agents for the treatment of patients with infections, although they only represent a partial approach to the problem. Over the last four decades, studies into the effects of AM use for severe infections by gram-positive or gram-negative bacteria have demonstrated a considerable reduction in the morbidity and mortality of populations affected by them.[18] Antimicrobial can be of more use for the treatment of early clinical stages of sepsis, before the host begins sequential mediator production resulting in more advanced inflammatory cascade stages with severe tissue damage resulting.[18] However, some authors have raised the idea that AMs may exacerbate the inflammatory response due to destruction of the microorganisms, liberating material from their cell walls and causing endogenous inflammatory mediators.[2]

Empirical AM treatments have been recommended, in particular for patients with sever sepsis and septic shock. Antimicrobial developed during the last decade, from the carbapenem group (imipenem and meropenem), and third and fourth generation cephalosporins have been proposed as monotherapy to replace aminoglycosides associated with a ß-lactamic for severe sepsis and septic shock. Recommendations indicate the use of wide spectrum penicillin AMs (associations with ticarcillin or piperacillin), of monobactam (aztreonam) or of quinolones, in combined empirical therapies.[18]

The removal or drainage of the infectious focus (e.g. peritonitis, empyema, septic osteoarthritis, necrotized tissues), and equally the removal of infected foreign bodies (including invasive devices), are important and relevant to stopping infectious stimuli, since such measures would tend to reduce or end the production of endogenous sepsis mediators, with a resultant reduction in the self-sustaining potential of the systemic inflammatory response.

Treatment aimed at improving innate immunity

One attempt to improve the efficiency of antibiotics is to increase innate immunity, by increasing the number of leukocytes. In a study by Rott et al., early use of filgrastim with adult patients, despite achieving the effect expected from the drug (increasing leukocytes to 75×10^9 cells/l), did not change patient 28-day mortality.[25]

Therapy aimed at the systemic inflammatory response

The majority of researchers agree that improved severe sepsis survival rates can only be achieved with additional therapies as well as conventional antimicrobial treatments. The more the complexity and interdependence of the pathophysiological mechanisms of sepsis are understood, the more therapeutic strategies based on substances which modulate or interrupt the effects of endogenous and exogenous sepsis mediators are sought.

The therapeutic strategy which appears to have the greatest chance of changing the disheartening results of sepsis treatment is to intervene at any point in sequence of pathophysiological events which characterize the systemic inflammatory response in sepsis, in order to modify (modulate) the host's reaction. Unfortunately, the clinical use of treatments which block individual mediators has failed to reduce the general mortality associated with sepsis (Table 2).

More than 30 randomized, blind trials involving 12,000 patients showed that the use of antibody blockers (platelet activation factor antagonist, antibradykinin, anti-prostaglandin, monoclonal anti-TNF antibody, IL-1 receptor antagonist, soluble TNF receptor, nitric oxide synthesis inhibitor) did not change the clinical course or mortality of patients with sepsis, and sometimes even compromised them.[26]

Agents which bond with or neutralize components in the bacterial cell wall (anti-endotoxin antibodies, lipopolysaccharide binding protein antagonist, CD14 receptor inhibitor, permeability-increasing protein antagonist) or those which modulate the immediate response of the host to these toxic products (pentoxifylline, amrinone) did not prove to be valid for sepsis treatment. The majority of studies realized to date did not reveal definitively negative results, but answers continue to be sought by means of better designed collaborative studies. A double-blind, randomized and controlled multicenter study of 847 patients at 53 hospitals in the USA, using two doses of monoclonal E5 antibody against endotoxin, demonstrated that there was no reduction in mortality among patients with sepsis from gram-negative germs with no shock, but that there was greater recovery from organ failure among these patients.[27] A more recent study, which used the human monoclonal antibody to a common enterobacteria antigen, also failed to reduce mortality.[28]

Pentoxifylline, in common with amrinone, inhibits phosphodiesterase, increasing concentrations of intracellular cyclic AMP, resulting in a reduction in cytokine accumulation, especially TNF-α. A European double-blind and randomized study of 100 newborns, demonstrated reduced mortality among premature sepsis patients within the group that received pentoxifylline, 5 mg/kg/h for 6 hours, on 6 consecutive days.[29]

Although, in theory, corticosteroids have always been considered to have some sort of cytokine synthesis blocking action, their use and efficacy for sepsis or septic shock have not been supported by clinical evidence and there are even studies that suggest their use may be prejudicial to these patients.[30] More recently, interest has once more increased in using corticosteroids for sepsis. The observation that

Table 2 - Therapeutic strategies for sepsis

Target	Agent	Type of crisis
Endotoxins	monoclonal antibodies	neutralizing or opsonizing effect
LPS-LBP complex	antibodies anti-LBP, BPI protein	↓ activation of macrophages induced by LPS; blockage of LPS-induced inflammatory response
TNF	monoclonal antibodies antiTNF; soluble tumour necrosis factor receptors	binding and inactivation of TNF- α; binding of free TNF- α
Interleukin-1	Interleukin-1 receptor antagonist	interference with the IL-1 binding receptor
Cytokines/ circulating toxins	corticosteroids, pentoxifylline, amrinone ECRM	blockage of TNF synthesis; exogenous depuration cytokines/circulating toxins
PAF	platelet activating factor antagonists, platelet activating factor acetylhydrolase, phospholipase A2 inhibitor	interference with PAF binding receptor ↓ PAF levels and leukotrienes
Thromboxane	dazoxiben, ketoconazole	inhibition of synthase thromboxane
Nitric oxide	NO synthesis inhibitor (N-methyl-L-arginine)	reduction in the production of NO
Oxygen free radicals	N-acetylcysteine, selenium, vitamin C and E	inativation/reduction in production of oxygen free radicals
Arachidonic acid metabolites	indometacin, ibuprofen leukotrienes receptor antagonist	inhibition of the cyclooxygenase and lipoxigenase pathway; blockage of prostaglandins receptors
Coagulation	antithrombin III, tissue factor pathway inhibitor, activated protein C	anticoagulation, ↓ proinflammatory mediators, inhibition/activation of neutrophils, ↓ production, ↓ platelet activation
Cytokines, immunity	immunoglobulins, interferon-γ, G-CSF	

Modified from Sáez-Llorens X et al.[2] and Bochud PY.[15]
LPS: lipopolysaccharide, LBP: lipopolysaccharide binding protein, BPI: bactericidal permeability-increasing, TNF: tumour necrosis factor, IL-1: Interleukin-1, ECRM: extracorporeal replacement methods, PAF: platelet activating factor, NO: nitric oxide, N-methyl-L-arginine: competitive inhibitor of nitric oxide synthetase, G-CSF: granulocytes colony-stimulating factor.

severe sepsis may be associated with relative adrenal insufficiency or resistance to glucocorticoid receptors induced by systemic inflammation has awoken interest in studies which evaluate the usefulness of low dose corticoids in sepsis situations. A randomized, double-blind, placebo-controlled study carried out by Annane et al., indicated that extremely ill patients with sepsis and persistent shock, requiring vasopressors and mechanical ventilation, benefited from the use of physiological doses of corticosteroids for 7 days, with reductions in duration of com vasopressor use and mortality rate when compared with the controls.[31] Similarly, a recent randomized, double-blind, placebo-controlled study by Keh et al., indicated that continuous, low dose, hydrocortisone use was of benefit to patients in septic shock, restoring hemodynamic stability when compared with controls.[32]

Agents which neutralize or prevent the action of inflammatory cytokines on their respective receptors, such as monoclonal anti-TNF-α antibodies tend to reduce the production of the next mediators in the inflammatory cascade (interleukin-1 [IL-1] and interleukin-6 [IL-6]), would hypothetically prevent pathophysiological damage, improving survival rates. A randomized, double-blind and controlled multicenter study of 1,879 patients at 105 hospitals in the USA and Canada, using murine monoclonal antibodies for TNF-α (TNF-α Mab), did not reveal differences in 28-day mortality between patients who had received the antibody and those who had received placebos.[33] Another randomized, double-blind and controlled multicenter study of 498 patients at 44 hospitals in the USA and Europe, receiving soluble TNF-α receptor fusion protein (p55), also failed to reveal reduced mortality among those who received

the antibody in comparison with those who received the placebo.[34]

Interleukin-1 receptor antagonist tend to attenuate hemodynamic alterations, reducing the severity of lactic acidosis and improving survival rates. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group, by means of a randomized, double-blind and controlled multicenter study of 696 patients at 91 hospitals in the USA and Europe, did not demonstrate reduced mortality with the use of human recombinant IL-1 receptor antagonist when compared with a placebo.[35]

Platelet activation factor, PAF, is a phospholipid produced by macrophages, neutrophils, platelets and endothelial cells, which can mediate the effects of innumerable cytokines. Thus, PAF receptor antagonists may be useful for treating sepsis due to gram-negative. A randomized, double-blind and controlled multicenter study of 600 patients with severe sepsis which tested PAF receptor antagonist for four days, did not demonstrate any reduction in mortality rate.[36]

It is now known that nitric oxide production, (NO endogenous vasodilator), is responsible for some of the harmful effects of the inflammatory response on target organs (vasodilation and hypotension; myocardial depression in septic shock). It is produced from L-arginine with the aid of NO synthase (NOs) and its inhibition or blockage is a therapeutic strategy to minimize these effects. Although its inhibition in animals with sepsis can lead to arterial pressure normalization, may result in other undesirable effects (e.g. reduced cardiac index and increased pulmonary pressure). It is thought that inhibiting NOs - L-NAME (N-nitro-L-arginine methyl ester) would also inhibit the beneficial effects of NO, and that only in situations of NO overproduction could this agent have any real benefit. The strategy of employing NOs inhibitors has not been sufficiently tested on humans.

The process of PMN activation and degranulation caused by inflammatory mediators results in large scale free radical production. It is believed that endogenous antioxidants (vitamins C and E, ß-carotene, catalase and superoxide dismutase) would not be sufficient to neutralize this exposure to free radicals and avoid cellular damage in SIRS. Studies of sepsis in animal models have shown beneficial effects from treatment with substances to scavenge oxygen free radicals (superoxide dismutase and catalase).[2,24] Other treatments with antioxidant agents (a-tocopherol, dimethyl sulphoxide, Q10 coenzyme, N-acetylcysteine, glutation, allopurinol, among others) are being evaluated in animal tests; results are so far inconclusive.

It is believed that products of the metabolism of arachidonic acid, by both routes (cyclooxygenase and lipooxygenase), and also prostaglandins and thromboxanes appear to perform a considerable role in target organs when the inflammatory response evolves and there is organ dysfunction. A number of different cyclooxygenase inhibitors (indomethacin, ibuprofen) appear to have beneficial effects at specific points in the inflammatory cascade and on the survival of animals. A randomized, double-blind and controlled multicenter study of ibuprofen with 455 sepsis patients revealed reduced prostacyclin and thromboxane levels, reductions in fever, tachycardia, lactic acidosis and oxygen consumption, but without preventing the development of shock or respiratory distress syndrome or improving patient survival.[37] A study by Arons et al. of patients with hypothermal sepsis, compared with febrile patients, demonstrated reduced mortality among patients treated with ibuprofen.[38] The majority of therapeutic strategies with non-steroidal antiinflammatories, both those attempted to date and those which are still under investigation have failed to produce definitively positive results for treatment of severe sepsis and septic shock. A meta-analysis of 18 clinical trials at phases II and III on the use of non-steroidal agents with antiinflammatory properties for sepsis treatment, based on 6,429 patients, demonstrated that there were only beneficial tendencies without significantly altering mortality.[3]

Heparin has also been studied for sepsis treatment, for its immunomodulatory properties and because, *in vitro* it inhibits the bond between L- and P-selectin, based on the observation that rats that are deficient in L-selectin are immune to lethal endotoxemia. In a randomized, double-blind, placebo-controlled study, Derhaschnig et al. tested non-fractioned heparin and low molecular mass heparin, after lipopolysaccharide infusion on healthy volunteers The group that received non-fractioned heparin, there were significant reductions in lymphocytopenia and in L-selectin down-regulation induced by the toxin, providing evidence that heparin has a probable mechanism of action of use in the treatment of sepsis.[39]

Another anticoagulant which has been investigated for sepsis treatment is antithrombin, which combines two effects: in addition to being an anticoagulant it also has antiinflammatory effects, inhibiting proteases which interact with cells that liberate proinflammatory mediators. The bond with syndecan-4 receptors interferes with intracellular signals induced by mediators such as lipopolysaccharide. It has been described as being of benefit in small cohorts of septic patients with coagulation disorders.[40] However in a large phase III multicenter, double-blind, placebo-controlled trial (KyberSept Trial), involving 2,314 adults with severe sepsis, the use of antithrombin III started within the first 6 hours did not reduce 28-day mortality (primary objective) or at 56 and 90 days (secondary objective). When the sample was stratified for concurrent heparin and antithrombin use, there was no difference in 28-day mortality, but 90-day mortality was significantly less for the group that did not receive heparin.[41] Concurrent heparin use, in addition to producing m ore hemorrhages, may have reduced the antiinflammatory effect of antithrombin. Later, Hoffmann et al. demonstrated that, in a laboratory, the of use antithrombin prevented, to a significant extent, endothelium-

leukocyte interaction and capillary damage, in animal sepsis models from lipopolysaccharide injection; however, among the animals that received antithrombin associated with heparin, lesions were similar to those that occurred in the controls (that had only received the toxin), thus demonstrating the adverse effects of associating the two drugs.[42] A multicenter, observational study, carried out in Italy with 216 patients who received antithrombin for sepsis, CIVD and other clinical conditions also concluded that this therapy did not benefit the sepsis patients in terms of mortality. In this sample there was no difference linked to concurrent heparin use.[43]

One treatment that has shown promise for sepsis appears to be recombinant human active C protein, or drotrecogin-α. Active C protein is an endogenous protein which promotes fibrinolysis and inhibits thrombosis and inflammation. In sepsis, because of the effects of inflammatory cytokines, there is a reduction in the conversion of inactive C protein into active C protein. The antiinflammatory effect of drotrecogin can come directly from the inhibition of neutrophil activation, from the production of cytokines induced by lipopolysaccharides, and from activated cell adhesion to the endothelium. The effect can also be indirect, by means of inhibiting thrombin generation, which leads to reduced platelet activation, neutrophil recruitment and labrocyte degranulation. In a randomized, multicenter, double-blind, placebo-controlled trial of continuous drotrecogin-α (Xigris©; Eli Lilly Co) for 96 hours or placebo, in 1,690 patients with severe sepsis, overall mortality was lower at 28 days among the treated group, representing a reduction of 6.1% in the absolute risk of death.[44] The drug was cleared for use on the basis of this single trial. Due to its potential to cause severe hemorrhages and its high cost, it has been recommended that patients be extremely carefully selected before receiving this treatment.[45,46]

It has been observed that many critical patients, even those who are not diabetic, have hyperglycemia and a reduced response to endogenous insulin, possibly because of increases in the levels of insulin-like growth factor binding protein. The use of exogenous insulin to maintain glycemia within normal parameters has proved to be of benefit, in terms of outcome, with patients suffering from myocardial infarction. There is a hypothesis that in sepsis, normoglycemia restores neutrophil phagocytic capacity, compromised by hyperglycemia. Another potential mechanisms is the antiapoptotic effect of insulin from activation of the phosphatidylinositol 3-kinase-Akt pathway.[1,22] Based on these principles, a randomized, controlled, prospective study was conducted of 1,548 adult patients post heart surgery, on mechanical ventilation. The control group received insulin infusion, when necessary to maintain glycemia between 180 and 220 mg/dl, while the treatment group received systematic insulin in order to maintain normoglycemia (glucose between 80 and 110 mg/dl). The treatment group had reduced 5-day mortality by 32% (primary objective) and also lower mortality during hospitalization, lower multiple organ failure mortality and fewer sepsis episodes (secondary objectives).[47]

Another strategy which has been suggested and has already won a place among sepsis treatment strategies use the techniques of extracorporeal substitution, such as continuous arterio-venous hemofiltration and plasmapheresis, especially in cases of severe sepsis and MOFS. They may be used at any phase of the inflammatory process with the objective of reducing concentrations of inflammatory cascade inflammatory mediators (exogenous and endogenous), and consequentially their potential to cause damage to target organs. A multicenter, randomized and controlled, multicenter clinical trial at seven tertiary ICUs with 30 patients with sepsis subjected to continuous plasmapheresis for 34 hours, only found attenuation of the acute phase sepsis response and a reduced tendency to organ failure, but with no effect of cytokine response or on final mortality.[48] A randomized and controlled clinical trial involving 106 adult patients with severe sepsis or septic shock, showed that the group treated with plasmapheresis had a mortality rate 28 days after discharge that was 20% lower than the control group that received standard treatment for shock.[49]

Despite some initially encouraging results, the majority of research into substances that are inflammatory reaction modulators failed to effectively reduce mortality. The reasons postulated for this failure include disparities between animal models and clinical reality, the heterogeneous nature of the patients and their manifestations of sepsis, and the complexity of the inflammatory cascade.[50]

Other potential therapies

Innumerable new agents appear to be effective in animal models, creating new hope for sepsis treatment. Interferon-γ has been considered capable of restoring macrophage HLA-DR expression and TNF-α production in patients with sepsis. The administration of antibodies against products of C5a activation reduced the frequency of bacteremia, preventing apoptosis and improving survival. The administration of antibodies against macrophage migration inhibitory factor protected rats from peritonitis. Strategies to block lymphocyte or gastrointestinal epithelial cell apoptosis have improved survival rates in experimental sepsis models.[1]

Concluding, we can state that, despite the diagnostic technological advances of recent years, little progress has been achieved in terms of changing the mortality of sepsis. This is due to the complexity of aggressor-host relationships, which cannot be regulated and whose modulation depends much more on host response than on therapeutic intervention. Certain strategies are certainly of benefit, such as early recognition of sepsis, aggressive initial intervention against hemodynamic disturbances

and rational handling of antimicrobial. Any advance in the understanding of the these three strategies will undoubtedly increase the chances of a good prognosis, although it is not expected that the increase would be of any great magnitude. The combination of immunomodulatory therapies appears to be the future for research in this area. Corticoid use, for patients with or without adrenal insufficiency is resurfacing as a promising strategy. Similarly, drotrecogin-a appears to be the only substance which has demonstrated an impact on mortality, although in an unexceptional manner. Nevertheless, we recommend caution with the initial enthusiasm about drotrecogin, taking into account the fact that since the publication of the original experiment there has been no reproduction of the research in a different scenario. Because of the peculiarities of children, the scarcity of studies and the complexity of sepsis in this age group, pediatricians should be alert to new discoveries in this area.

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