

REVIEW

New therapeutic alternatives for severe sepsis in the critical patient. A review[☆]

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KEYWORDS

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Abstract

Background: Despite efforts to establish uniform protocols for the management of severe sepsis, this condition continues to have high morbidity and mortality. This is due, among other factors, to the many barriers for the development of the protocols and the application time. That is why new therapeutic measures are continuing to be investigated and developed.

Objective: To review the literature on the new and future therapeutic alternatives available in the management of sepsis in critically ill patients.

Data source and search method: A search was made for articles consistent with evidence-based medicine guidelines published between 2004 and 2009 in different databases (Cochrane Plus Library, National Guideline Clearinghouse, Clinical Evidence, REMI and PubMed) and the NIH Clinical Trails database (ClinicalTrials.gov) using the TRIP meta-search engine.

Study selection: A total of 357 documents were retrieved, selecting 48 of which included systematic reviews, meta-analyses, clinical practice guidelines, structured abstracts of original articles, and clinical trials. The selection criteria followed the peer review process.

Data extraction: Data were extracted by two independent reviewers.

Conclusions: Based on the 2004-2009 study period, sufficient evidence was not obtained to make further recommendations on the treatment of sepsis. Although the abundant evidence needed to suggest the utility of these therapeutic measures, inhaled nitric oxide, statins, and immunoglobulins are probably good options for the adjuvant treatment of sepsis. However, we must wait for the results of different ongoing clinical trials on new treatment modalities. Stem cells and gene therapy will probably emerge as novel therapies in the future.

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PALABRAS CLAVE

Nuevas terapias;
Sepsis;
Paciente crítico

Nuevas alternativas terapéuticas para la sepsis grave en el paciente crítico. Revisión**Resumen**

Introducción: La sepsis grave sigue teniendo elevadas morbilidad y mortalidad, a pesar de los esfuerzos realizados en la instauración de protocolos uniformes de actuación, debido, entre otros muchos factores, a la existencia de múltiples barreras para la implantación, así como su tiempo de aplicación. Es por ello que se sigue desarrollando e investigando sobre nuevas medidas terapéuticas.

Objetivo: Realizar una revisión de la literatura sobre las nuevas y futuras alternativas terapéuticas de que disponemos para el tratamiento de la sepsis en los pacientes críticos.

Fuentes de datos y método de búsqueda: Se llevo a cabo una búsqueda limitada por tiempo desde 2004 hasta 2009, a través del metabuscador Trip Database en las páginas de medicina basada en la evidencia (Cochrane Plus, National Guideline Clearinghouse, Clinical Evidence, REMI y PubMed) y base de datos de ensayos clínicos (ClinicalTrials.gov).

Selección de los estudios: Se obtuvieron de la búsqueda 357 documentos, de los cuales se seleccionaron 48 que incluyen revisiones sistemáticas, metaanálisis, guías de práctica clínica, resúmenes estructurados de un artículo original y ensayos clínicos. El método empleado para aplicar estos criterios se hizo mediante una revisión por pares.

Extracción de datos: Un posterior análisis por dos revisores independientes.

Conclusiones: En el periodo de estudio 2004-2009 no ha habido aportaciones con evidencia suficiente como para realizar nuevas recomendaciones en el tratamiento de la sepsis. Aunque no se aporta la abundante evidencia que señale la utilidad de estas medidas terapéuticas, probablemente el óxido nítrico inhalado, las estatinas y las inmunoglobulinas sean buenas alternativas en el tratamiento adyuvante de la sepsis. Tendremos que esperar, de todas maneras, los resultados de los diferentes ensayos clínicos que se encuentran en marcha sobre las nuevas terapias. El futuro posiblemente podría estar en las células madre y la genoterapia.

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Introduction

Sepsis remains an important problem in terms of incidence and mortality, which reaches over 40% in cases of severe sepsis or septic shock, despite the efforts made to introduce uniform intervention protocols.

In the year 2002, the different scientific societies (American Association of Critical-Care Nurses, American College of Chest Physicians, American College of Emergency Physicians, American Thoracic Society, Australian and New Zealand Intensive Care Society, European Society of Clinical Microbiology and Infectious Diseases, European Society of Intensive Care Medicine, European Respiratory Society, Infectious Disease Society of America, International Sepsis Forum, Society of Critical Care Medicine, Surgical Infection Society), being aware of this situation, launched a campaign (posteriorly revised in 2004 and 2008^{1,2}) referred to as the "Surviving sepsis campaign". The great advance resulting from this campaign has been the application of a series of measures in accordance to the time elapsed. Thus, the resuscitation package of measures, corresponding to the first 6 hours, includes the determination of lactate and the administration of antimicrobials (following extraction for blood cultures) in the first hour or 3 hours, with adequate volume replacement, vasopressors, central venous pressure (CVP) > 8 mmHg and SvO₂ > 70%. Likewise, a package of measures is recommended in the first 24 hours, involving the administration of hydrocortisone and activated protein C (APC), with median blood glucose < 150 mg and mechanical ventilation with a median plateau pressure of < 30 cmH₂O.

In this same sense, the Spanish Society of Emergency Care Medicine (*Sociedad Española de Medicina de Urgencias y Emergencias*, SEMES) and the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (*Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias*, SEMICYUC), being aware of the problem, jointly drafted a consensus document with the purpose of developing an intervention guide to facilitate the early identification and management of septic patients.³

At present there is sufficient scientific evidence to affirm that the early and guided application of a series of diagnostic and therapeutic measures—including effective antibiotic treatment, adequate goal-oriented hemodynamic resuscitation, or the use of activated protein C in the more seriously ill patients—significantly improves survival.^{4,5} It is also known that adherence to these measures is poor in all hospital settings.⁶

On the other hand, and since there is continued development and research in relation to new therapeutic measures, the present study was designed to offer a review of the literature on the new and future therapeutic alternatives that will become available for the treatment of severe sepsis in non-neutropenic adult critical patients.

Material and method**Search strategy**

In October 2009 a review was made of the data sources, using the following terms and keywords: new therapy AND

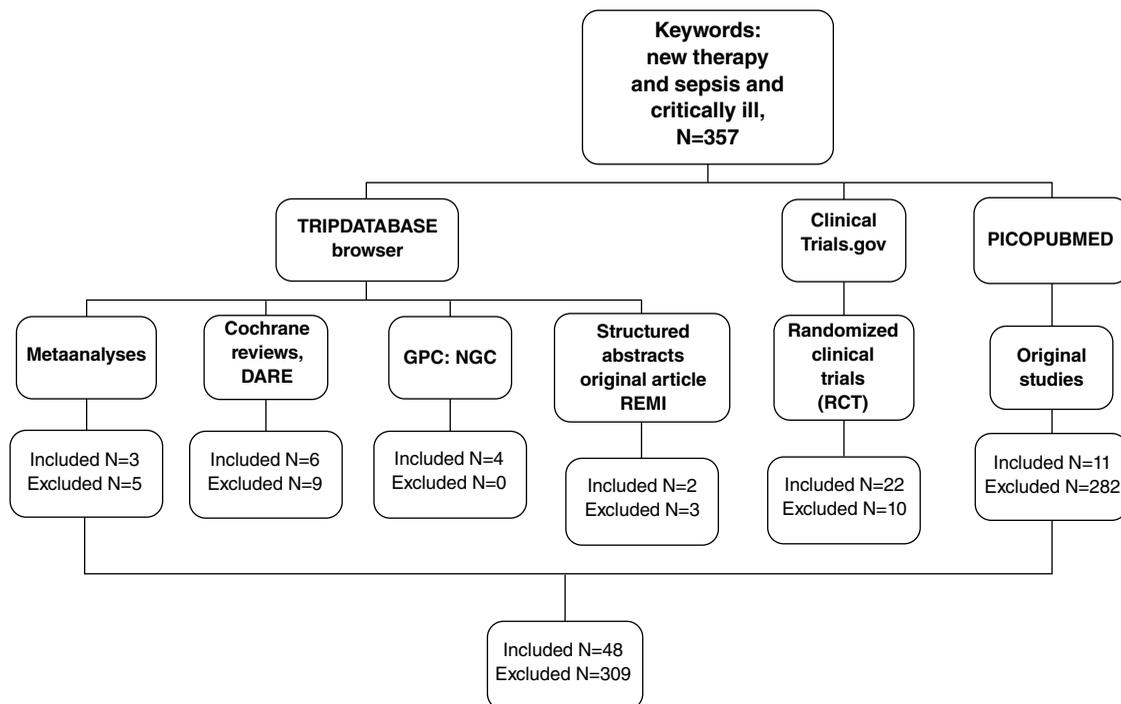


Figure 1 Flowchart: Search strategy. Exclusion criteria: therapies not contemplated in sepsis and irrelevant to the effects of our study, articles referred to the neonatal or pediatric population, duplicated studies included in metaanalyses, developed reviews and structured abstracts, retrospective cohort studies, clinical cases, laboratory studies and not well defined therapies. DARE: Center for Reviews and Dissemination; CPG: clinical practice guide; NGC: National Guideline Clearinghouse.

sepsis AND critically ill, limited in time from 2004 to 2009, published in English, and using the metabrowser Trip Database in the medical pages based on evidence (Cochrane Plus, National Guideline Clearinghouse, Clinical Evidence, REMI, PubMed) and clinical trials database, ClinicalTrials.gov. In the selection of the studies we recorded 357 documents, of which 48 were selected, including systematic reviews, metaanalyses, clinical practice guides, structured abstracts of original articles, and clinical trials. We excluded articles involving therapies not contemplated in sepsis and irrelevant to the effects of our study, articles referred to the neonatal or pediatric population, duplicated studies included in metaanalyses, developed reviews and structured abstracts, retrospective cohort studies, clinical cases, laboratory studies or not well defined therapies, as shown in the flowchart (Fig. 1).

The method used to apply these criteria was peer review, and data extraction was carried out with posterior analysis by two independent reviewers.

Search results

Incidence-mortality, non-compliance and economical implications of the implantation of a sepsis protocol

The publication of Iñigo et al.⁷ was the first population-based study in Spain to describe the epidemiology of severe sepsis in the Community of Madrid—estimating its incidence, mortality and impact upon stay and costs. The information

source was the minimum basic data set of the Community of Madrid corresponding to the year 2001, and a total of 6968 episodes were identified. The authors concluded that severe sepsis is a frequent condition with high mortality and an important impact in terms of healthcare resource consumption.

Posteriorly, Esteban et al.⁸ published the first analysis in Spain of the population-based incidence and mortality of sepsis. The study involved a prospective cohort design, and confirmed the high incidence of the disorder (73-31 cases per 100,000 adults and year in reference to severe sepsis and septic shock), with an in-hospital mortality rate of between 20.7-45.8%. Many of these patients with severe sepsis and septic shock were treated outside the Intensive Care Unit (ICU), and only 12% of all stages were admitted to the ICU.

At the same time, studies were made to evaluate compliance with the therapeutic measures and their economical impact. In this context, the observational study published by De Miguel et al.,⁹ involving a single center, had the primary objective of evaluating compliance with the measures developed to optimize the treatment of severe sepsis in our routine clinical practice—attempting also to identify the variables significantly associated with patient mortality. The authors concluded that the packages of measures proposed in the “Surviving sepsis campaign” do not seem to have had sufficient impact in our Emergency Departments, and that this may constitute a starting point for planning a process designed to improve the prognosis of patients with severe sepsis in our hospitals.

In the United States, Carlson et al.¹⁰ conducted a telephone survey of the medical personnel and nursing

supervisors of 100 hospital Emergency Departments. Only 7% of these Departments applied the goal-oriented early resuscitation protocol in severe sepsis. In order to improve the quality of resuscitation in severe sepsis, it is necessary to identify the barriers that complicate adherence. The mentioned survey identified the main problems: a lack of nursing personnel, the impossibility of monitoring central venous pressure, limitations in physical space, and difficulties in identifying patients with severe sepsis.

Shorr et al.¹¹ examined the economical implications of the introduction of a severe sepsis protocol in the context of a non-randomized study with a limited number of patients (n=120), involving a single center. Despite the limitations of the study, it was shown that the application of a protocol for the management of septic shock in the emergency room not only reduces mortality but is also cost-effective and allows the saving of resources.

What do we have since the “Surviving sepsis campaign”?

The EDUSEPSIS study, carried out by Ferrer et al.,⁶ demonstrated improvement in the care and prognosis of severe sepsis patients after an educational program in Spain, based on the “Surviving sepsis campaign”. The authors concluded that the improvement process based on the best scientific evidence, and its transfer reflected in recommendations and clinical guides, does not automatically ensure improvement in the treatment of patients. Measures must be introduced to guarantee that the clinical guides are actually put into practice. This requires the auditing of compliance with the standards of care and the putting into practice of educational, training and facilitation measures. This ambitious study, put into practice throughout the country, reflects the difficulties involved in applying the clinical guides, and points to the need to maintain the learning process over time.

Posteriorly, these same authors,¹² in the context of the same EDUSEPSIS project, analyzed the efficacy of the treatments recommended in the “Surviving sepsis campaign”, based on the data of 2796 patients with severe sepsis in 77 ICUs, and registering compliance with four treatments—the analysis being fundamented upon a multiple logistic regression model and the propensity score. The study concluded that only in severe sepsis, the treatments associated to lesser in-hospital mortality were the early administration (in the first hour) of a broad-spectrum antibiotic in all patients (OR [95%CI] = 0.87 [0.5-0.9]; $p < 0.008$), and the administration of activated drotrecogin alpha in multiorgan failure (OR [95%CI] = 0.59 [0.41-0.84]; $p < 0.004$).

Supportive treatment of severe sepsis ([Table 1] and [Table 2])

Hemodynamic aspects: vasoactive drugs

Vasoactive drugs are one of the key elements in the treatment of septic shock. The current treatment guides in cases of shock point to dopamine and noradrenalin as the first choice agents, with no clear evidence of the superiority of one drug over the other. No clinical trials have compared the two substances, though most observational studies have associated dopamine with increased mortality.

The randomized, prospective, double-blind multicenter clinical trial published by Annan et al.¹³ compared the efficacy and safety of adrenalin with the combination of noradrenalin and dobutamine. The choice of one regimen or the other does not seem to require modifications in the light of the findings of this study. The use of adrenalin, on the other hand, may prove much more complicated outside the controlled context of a clinical trial.

Given its importance, and although it falls outside the search limits of our review, mention should be made of the recent study carried out by De Backer et al.¹⁴ This is a multicenter trial involving 1679 patients with shock of any origin (including septic shock), randomized to receive as first choice drug either dopamine (at a dose of up to 20 µg/kg/min) or noradrenalin (at a dose of up to 0.19 µg/kg/min). The patients that failed to respond to these doses received noradrenalin, vasopressin or adrenalin. The primary efficacy endpoint was mortality after 28 days. Although the study found no differences in mortality between the patients treated with dopamine and those administered adrenalin, there was a nonsignificant tendency towards lesser mortality with noradrenalin. Dopamine was associated with a greater frequency of tachycardia and severe arrhythmias, and with greater mortality in the subgroup of patients with cardiogenic shock. Based on these data, noradrenalin should be regarded as superior to dopamine, and therefore should be defined as the first choice drug in shock patients.

A phase III clinical trial is currently in course to compare the efficacy of levosimendan versus dobutamine in patients with septic shock—the primary objective being the resolution of shock, and the secondary objective the changes in cardiac function. This study is currently in the patient recruitment phase.¹⁵

Acute renal failure and extrarenal filtration

Septic shock is a frequent cause of multiorgan failure (MOF) in the ICU. For this reason extracorporeal techniques for the management of renal failure have become generalized in such Units, and at the same time new extracorporeal filtration systems have been developed for the elimination of inflammatory mediators.

Latour et al.¹⁶ have published an excellent critical review of the optimum dialysis dose in acute renal failure, analyzing the effectiveness of high doses in comparison with the traditional doses in patients with acute kidney damage, in terms of mortality and the recovery of renal function—based on the Vicenza, ATN and DOREMI studies. The results of this review point to the existence of firm evidence that high-volume hemofiltration (HVHF) does not significantly reduce mortality in renal failure patients. Indeed, there are even indications that HVHF may be deleterious for patients with sepsis and renal failure (DOREMI, adjusted OR (95%CI) = 1.91 [0.71-5.13]). There is moderate evidence that high doses do not improve the recovery of renal function in patients with acute renal failure (RR [95%CI] = 0.96 [0.88-1.05]); as a result, given the associated increase in work load and costs, the recommendation of HVHF in these patients is not justified. The recommendations on the use of high doses in patients with severe sepsis without renal failure, or the possible usefulness of pulse HVHF in patients with inflammatory response syndrome and hemodynamic instability, were outside the scope of the mentioned review.

Table 1 Update on new alternative therapies in sepsis

Study	Therapy
Jaime Latour-Pérez, 2009 ¹⁶	Extrarenal filtration
Dinna N. Cruz, 2009 ¹⁷	Polymyxin B
Donald E.G. Griesdale, 2009 ²⁰ ; Wiener R.S., 2009 ²¹	Insulin
ATS2005, Eid 2008 ^{22,23} ; Martí-Carvajal, 2008 ²⁵	Coagulation: ATIII, IFT, APC
D. Annane, 2009 ²⁹	Corticosteroids
Gómez-Tello, 2008 ³⁶	Immunoglobulins
Edwin Massey, 2009; Smith, 2006 ^{37,38}	Colony stimulating factor
Wang, 2009 ³⁹	HMGβ1
Weil, 2009 ⁴³	Stem cells
Wurfel, 2009 ⁴⁴	Polymorphisms

New extracorporeal filtration techniques have recently been developed for the elimination of inflammatory mediators, such as hemoperfusion with polymyxin B and plasmapheresis.

Hemoperfusion with polymyxin B

For years, the early utilization of hemoperfusion with polymyxin B in septic shock of abdominal origin forms part of standard treatment for sepsis caused by gram-negative bacilli in Japan. The mechanism involves the elimination of endotoxins through adsorption, preventing progression of the inflammatory cascade. In this sense, Cruz et al.¹⁷ have recently published a randomized clinical trial to determine the efficacy of hemoperfusion with polymyxin B—the clinical endpoints being a lesser use of vasopressors, arterial oxygen tension/inspiratory oxygen fraction, SOFA (Sequential Organ Failure Assessment) score, and mortality due to sepsis caused by gram-negative bacilli. They included 64 patients with severe sepsis and septic shock of abdominal origin subjected to emergency management. The trial was stopped by the ethics committee once the first 64 patients had been recruited, due to the evidenced differences in mortality. The SOFA score and survival rates were better in the polymyxin B group. The results of this clinical trial are scantily extrapolatable to other types of septic patients, however, since these were highly selected patients in which elimination of the primary focus proved possible.

Plasmapheresis

Based on previous studies such as the work of Busund et al.,¹⁸ where there appeared to be a tendency towards diminished mortality, new techniques have been developed, such as CPFA (coupled plasma filtration adsorption), which uses a plasma-blood separation adsorbent, obtained with a plasma filter. The COMPACT clinical trial,¹⁹ which is currently in the patient recruitment phase, aims to determine whether the combination of plasma, filtration and adsorption is able to reduce mortality and prevent organ failure in septic shock.

The treatment consists of the separation of plasma from blood with adsorption of the inflammatory mediators and cytokines from plasma, followed by a purification phase using a hemofilter. It possibly may be more useful in selected cases with thrombocytopenia, and caused by gram-negative bacilli.

Metabolic aspects: nutrition in sepsis, insulin

In the meta-analysis published by Griesdale and Wiener^{20,21} on the use of intensive insulin therapy and the reduction of mortality in critical patients, which included the data of the NICE-SUGAR, intensive insulin therapy was seen to significantly increase the risk of hypoglycemia (OR [95%CI] = 5.99 [4.47-8.03]), and afforded no benefits in terms of global mortality among the critical patients (OR [95%CI] = 0.93 [0.83-1.04]). Such treatment may benefit patients admitted to a surgical ICU (OR [95%CI] = 0.63 [0.44-0.91]).

Hematological aspects: coagulation

Strategies designed to restore the physiological anticoagulant pathways, such as the administration of antithrombin (ATIII) and anti-tissue factor, have been developed in patients with severe sepsis/ septic shock in recent years.

A review conducted by the American Thoracic Society on anticoagulant treatment with antithrombin III and tifacogin (anti-tissue factor) has concluded that both strategies proved ineffective in reducing mortality in two large placebo-controlled, phase III trials.²²⁻²⁴

Adjuvant treatment of severe sepsis

Activated protein C (APC)

The clinical practice guides recommend the administration of activated protein C (APC), in adult patients with severe sepsis and a high mortality risk, defined by any of the following four criteria:

1. Acute dysfunction of two or more organs
2. APACHE-II score > 24 points in the previous 24 hours
3. Septic shock
4. Acute respiratory distress syndrome (ARDS) secondary to sepsis ($pO_2/FiO_2 < 200$ mmHg)

Activated protein C is not indicated in either pediatric patients or in high risk adult patients (APACHE-II score < 25 points and failure of a single organ). The most serious adverse effect related to the administration of APC is bleeding.

Marti-Carvajal et al.²⁵ carried out a systematic Cochrane review on recombinant human activated protein C for severe sepsis, including the following four clinical trials:

Table 2 Randomized clinical trials presently in course, evaluating new alternatives in the treatment of sepsis

Therapy	ID	Phase	Start	Status	End	Sponsor	Collaborators
<i>Levosimendan</i>	NCT0093301	III	October 2004	Patient recruitment	Planned April 2006	Wentworth	Abbott
<i>Plasmapheresis (COMPACT)</i>	NCT00332371	III	December 2006	Patient recruitment	December 2010	Gruppo italiano per la Valutazione degli interventi en Terapia intensiva	Instituto Mario Negri of Pharmacological Research BELLO, Mirandola (MO), Italy
<i>APC (APROCCHS)</i>	NCT00625209	III	March 2008	Patient recruitment	March 2012	University of Versailles	Public Healthcare – Hospitals of Paris, Ministry of Health, France
<i>Nitric oxide</i>	NCT00608322	III	August 2009	Patient recruitment	December 2010	National Institute of General Medical Sciences (NIGMS)	
<i>Statins</i>							
<i>Rosuvastatin</i>	NCT00979121	III	December 2009	Not yet open	September 2012	National Heart, Lung and Blood Institute (NHLBI)	
<i>Simvastatin</i>	NCT00450840	IV	March 2007	Patient recruitment	Not planned	Medical University of Vienna	
<i>Selenium (SEPECT)</i>	NCT00832039	III	May 2009	Not yet open	August 2011	Kompetenznetz Sepsis	Biosyn, BrahmsAG
<i>EPA and GLA</i>	NCT00329680	IV	June 2007	Completed	October 2009	Fernandes Tavora Hospital	Abbott
<i>Anti-TF</i>	NCT00879606	II	April 2009	Patient recruitment	June 2010	Altor Bioscience Corporation	National Heart, Lung and Blood Institute (NHLBI)
<i>Lactoferrin</i>	NCT00630656	II	April 2008	In course	February 2010	Agennix	
<i>Vasoactive intestinal peptide</i>	NCT00004494	I	September 1998	Patient recruitment	Not planned	FDA Orphan Products Development Office	New York State University
<i>TAK-242</i>	NCT00143611	III	September 2005	Completed	February 2007	Takeda Global Research & Development Center, Inc.	

EPA: eicosapentanoic acid; GLA: gammalinolenic acid.

1. Abraham 2005: randomized, double-blind versus placebo trial. Multicenter: 516 centers, international with 34 countries and 2640 patients.
2. Bernard 2001a: randomized, double-blind versus placebo trial. Multicenter: 40 centers, international and 135 patients.
3. Bernard 2001b: randomized, double-blind versus placebo trial. Multicenter: 164 centers, international with 11 countries and 1728 patients.
4. Nadel 2007: randomized, double-blind versus placebo trial. Multicenter: 104 centers, international with 18 countries and 477 patients.

The review analyzed a total of 4911 patients (4434 adults and 477 pediatric patients) in relation to mortality after 28 days. APC was not seen to reduce the mortality risk in adults with severe sepsis (grouped RR = 0.92; 95% confidence interval, 0.72 to 1.18; $p = 0.50$, $I^2 = 72\%$). The effectiveness of APC did not seem to be associated to the severity of sepsis (two studies): for an APACHE-II score of < 25 points, the RR was 1.04 (95%CI, 0.89 to 1.21; $p = 0.70$), while in the participating patients with an APACHE-II score of 25 points or more, the RR was 0.90 (95%CI, 0.54 to 1.49; $p = 0.68$). However, the use of APC was associated to an increased risk of bleeding (RR = 1.48 [95%CI, 1.07 to 2.06; $p = 0.02$, $I^2 = 8\%$). Two studies were prematurely interrupted because there were few chances of reaching the expected efficacy at the end of the study –no evidence being found to suggest that APC should be used in the treatment of patients with severe sepsis or septic shock. In addition, the use of APC appears to be associated to an increased risk of bleeding.

Posteriorly, two phase III clinical trials were started, and are currently in the patient recruitment stage, with the purpose of evaluating the efficacy and safety of APC in adults with septic shock. The objective is to determine whether treatment with this drug reduces mortality in patients with septic shock, compared with placebo, in patients administered a standard treatment.²⁶

The APROCCHS clinical trial,²⁷ designed to compare the efficacy and safety of APC and low-dose corticosteroids, investigate the interaction between them in the management of septic shock, and assess reduction of mortality, is presently in the patient recruitment phase, and no results have yet become available.

Corticosteroids in severe sepsis and septic shock

The clinical trials carried out in recent years with hydrocortisone replacement doses in septic shock have shown such treatment to improve the patient hemodynamic condition and reduce mortality.

The results of the CORTICUS study,²⁸ a randomized, double-blind and placebo-controlled multicenter clinical trial in adult patients with septic shock for less than 72 hours, do not warrant the use of hydrocortisone in patients with septic shock. In this study the patients, after a standard ACTH test (250 µg), received 50 mg i.v. of hydrocortisone or placebo every 6 hours during 5 days, with gradual dose reduction over a further 6 days. The primary outcome endpoint was mortality after 28 days in the patients without response to the ACTH test. The results of this study do not support the use of hydrocortisone in septic shock, and do not demonstrate the usefulness of ACTH testing in

selecting patients who might benefit from this treatment. However, the lesser mortality of the patients of the CORTICUS study with respect to previous trials, and the more favorable hemodynamic response of those treated with hydrocortisone, indicate that the treatment may be beneficial in patients with an increased mortality risk –such as those with persistent hypotension despite the start of treatment with vasoactive drugs, or those who require progressively higher doses of such drugs.

In this context, the current international guides of the “Surviving sepsis campaign” indicate that knowing overinfection to be the main risk associated with corticosteroid use, the following recommendations of use can be made:

1. In adults with septic shock only when hypotension fails to respond to adequate fluid replacement and the administration of vasopressors.
2. ACTH testing is not recommended for selecting patients with septic shock who should receive hydrocortisone.
3. Hydrocortisone is preferable to dexamethasone.
4. Fludrocortisone can be included (50 µg via the enteral route once a day) if use is made of an alternative to hydrocortisone without mineralocorticoid activity. The use of fludrocortisone is optional if hydrocortisone is used.
5. Corticosteroid treatment can be reduced when the vasopressors are no longer needed.
6. The hydrocortisone dose should not exceed 300 mg/day.
7. Corticosteroids should not be used to treat sepsis in the absence of shock, unless the patient has endocrine antecedents or a history of corticosteroid use advising such treatment.

This new systematic review, carried out by Annane et al., and which includes the CORTICUS trial,²⁹ comprising 22 studies (17 randomized clinical trials in 2138 patients and 3 semi-experimental studies in 246 patients), investigates the effects of corticosteroids upon mortality after 28 days in patients with sepsis and septic shock (primary outcome endpoint) (OR [95%CI] = 0.87 [0.74-1.01]), as well as the effect of the dosage and duration of treatment upon different results. With these data in hand, it is not advisable to extend low-dose corticosteroid use to the full spectrum of patients with sepsis; rather, such treatment should be reserved for the more serious cases, in wait of the publication of the clinical trials that are still in course.

Miscellaneous: nitric oxide, statins, immunoglobulins and others

Nitric oxide

In a systematic review carried out by Centre for Reviews and Dissemination (DARE), in patients with respiratory distress syndrome secondary to sepsis with multiorgan failure, inhalatory nitric oxide did not appear to improve the results in this population; as a result, its utilization should be reconsidered.³⁰

In this context, a phase III clinical trial currently in the patient recruitment stage³¹ has been designed to determine whether inhalatory nitric oxide is effective in application to microcirculatory dysfunction and multiorgan failure (SOFA score) in the management of the early stages of sepsis.

Statins

There is growing debate about the possible role of the statins in the management of sepsis. Kopterides et al.,³² in a critical review of 22 studies involving 177,260 patients (7 prospective cohorts, 12 retrospective cohorts, 2 retrospective studies and one randomized clinical trial), concluded that most of the studies find the statins to exert a beneficial effect upon infection outcome. However, the observational nature of the survey precluded the drawing of firm conclusions.

Two phase III and IV clinical trials are currently underway on the use of simvastatin in patients with septic shock –the aim being to demonstrate the hypothesis that short-term therapy with simvastatin can improve the deleterious effects of acute vascular inflammation in patients with septic shock. The primary objective is the reduction of vasoactive drug use in cardiovascular support.³³

Another study attempts to evaluate the efficacy and safety of rosuvastatin 20 mg via the oral route or nasogastric tube during 28 days, or until hospital discharge, in patients with sepsis induced by acute lung damage, and its influence upon the reduction of mortality. No information in relation to the results is available.³⁴

Immunoglobulins

Laupland et al.³⁵ conducted a systematic review and metaanalysis of 14 randomized clinical trials involving 1987 patients, with the aim of determining whether adjuvant therapy with intravenous polyclonal immunoglobulin reduces mortality among adults with severe sepsis and septic shock. Pentaglobin was the immunoglobulin most often employed in the studies. This metaanalysis shows a global reduction in mortality with the use of intravenous immunoglobulin in the adjuvant treatment of severe sepsis and septic shock in adults, RR = 0.66 (0.53-0.83), though there is significant heterogeneity among the trials included, and this result was moreover not confirmed when the analysis was made in reference to the high quality studies.

Gómez³⁶ conducted a critical review of the use of immunoglobulins in septic patients, and on the basis of the evidence obtained proposed the use of immunoglobulin enriched with IgM / IgA as adjuvant therapy. It must be mentioned that the studies with a greater provision of IgM/ IgA and involving high doses were found to be more effective in reducing mortality. This would constitute grade C recommendation (based on several small randomized clinical trials with uncertain results), or grade 2C recommendation according to the GRADE scale.

Others: colony stimulating factor, HMGb1, antioxidants, stem cells and polymorphisms

Colony stimulating factor

The identified controlled trials raise the possibility that prophylactic granulocyte transfusions at a dose of at least 1×10^{10} could reduce the risk of mortality due to infection. The results of these trials reveal no reduction in global mortality. However, most of the studies were made decades ago, and the standard in supportive care have advanced considerably since then. It is difficult to recommend prophylactic granulocyte transfusions outside the context of the controlled trials currently in course, given the

implications in terms of resources and costs. Larger studies are needed to establish the validity of the potential benefits suggested by this review, in view of the methodological limitations, the small sample sizes, and the heterogeneous definitions of infection found in the included studies.^{37,38}

Antihydroxymethylglutaryl b1 antibodies (HMGβ1)

HMGβ1 are neutralizing antibodies that inhibit the inflammatory cascade. The review published by Wang et al.³⁹ discusses the potential therapeutic effect of a series of HMGβ1 inhibitors (neutralizing antibodies targeted to endotoxins) in experimental sepsis, though with scant possibilities for extrapolation to the clinical setting.

Antioxidants

Selenium. During sepsis and multiorgan failure, the serum concentrations of selenium – a glutathione peroxidase cofactor – are seen to decrease. A phase III clinical trial (SISPCT) has been planned with the aim of determining whether the intravenous administration of selenium is able to reduce mortality in patients with severe sepsis or septic shock. In addition, it is being examined whether the measurement of procalcitonin (PCT) can be used to guide the therapeutic measures.^{40,41}

Eicosapentenoic acid (EPA) and gammalinolenic acid (GLA). No data are yet available on a phase IV clinical trial that has just been completed, and which was started in June 2007 with the purpose of determining the possible role of an enteral formula enriched with EPA, GLA and antioxidants, versus a standard isocaloric diet. The authors have analyzed the impact of this diet upon the control of blood glucose and its capacity to prevent the progression of sepsis towards more serious conditions such as severe sepsis and septic shock.⁴²

Stem cells and polymorphisms. The experimental evidence indicates that stem cells are immunologically sensitive cells in sites of inflammation and tissue damage. These cells secrete growth factors in response to lipopolysaccharides and tumor necrosis factor, which may limit apoptosis and organ damage, and might represent an endogenous therapeutic strategy.⁴³ Likewise, variations in the common sequence of genes encoding for the innate immune response, inflammatory mediators and coagulation modulators have drawn special attention. The important information on the physiopathology of sepsis, provided by these studies, will be analyzed together with the relevance of such findings in relation to the design of future diagnostic and therapeutic strategies.⁴⁴

Clinical trials in course: anti-TF, lactoferrin, vasoactive intestinal peptide, TAK-242 (Table 2)

Anti-tissue factor

Tissue factor (TF) dependent upon the activity of procoagulating activity and the associated inflammatory processes may play a role in the severity and progression of acute lung injury, ALI/ ARDS. Recent studies have shown the levels of TF to be increased in plasma and lung edema fluid in ALI/ ARDS. This in turn was correlated to increased mortality, more days of ventilation, the presence of disseminated intravascular coagulation and sepsis in patients

with ALI/ ARDS. Therefore, antibodies that block TF activity may constitute an effective mechanism for the treatment of inflammatory disorders such as ALI and ARDS.

In this line there is a phase II clinical trial presently in the patient recruitment period, designed to evaluate the use of anti-tissue factor (anti-TF) antibodies (ALT-836) for the treatment of septic patients with acute lung injury or acute respiratory distress syndrome, assessing the safety and efficacy of a recombinant anti-TF antibody versus placebo in patients with sepsis and ALI/ ARDS.⁴⁵

Lactoferrin

Lactoferrin is a glycoprotein and a potent antioxidant which moreover possesses immune stimulating, antiviral and antimicrobial properties. It belongs to the cytokine family modulating the coordination of cellular immune response to infections. In this sense, there is a phase II clinical trial in course that aims to evaluate the safety and potential benefit of recombinant human lactoferrin (talactoferrin- α), 15 ml of a 100 mg/ml (1.5 g) oral solution administered three times a day for a maximum of 28 days or until discharge from the ICU, versus placebo, in patients with severe sepsis –the primary objective being the reduction of mortality.⁴⁶

Vasoactive intestinal peptide (VIP)

Vasoactive intestinal peptide is a 28-amino acid polypeptidic hormone with vasodilator activity and effects upon the peripheral nervous system. As an example, VIP relaxes the lungs, trachea and gastric muscle. It inhibits the secretion of gastric enzymes and stimulates the secretion of glucagon, insulin and somatostatin – increasing adenylyl cyclase and bile secretion in the liver.

A phase I study is presently being carried out on the intravenous dosing of VIP administered over 6 or 12 hours, in patients with respiratory distress syndrome and sepsis, with the purpose of evaluating the safety and pharmacodynamic activity of this peptide in patients of this kind.⁴⁷

TAK-242

A phase III clinical trial has been designed with the purpose of establishing the optimum dose of TAK-242 (a cytokine suppressor), administering 1.2 mg/kg as a subcutaneous injection over 30 min., and then TAK-242 at a dose of 0.05 mg/kg/hours (1.2 mg/kg/day) in the form of a subcutaneous injection during 96 hours versus placebo, with evaluation of the reduction in mortality among patients with sepsis.⁴⁸

Conclusions

The multiple studies made on the introduction of a sepsis intervention protocol offer clinical and economical benefits. It is necessary to analyze the local organizational barriers that prevent each hospital from applying such protocols. The two measures found to be most effective in these protocols, following the corresponding multivariate analyses, in terms of a reduction in patient mortality, are the early use of empirical broad-spectrum antibiotic treatment in all patients and the use of activated protein C in the more seriously ill subjects. However, these findings are based only on the data from a sub-analysis of an

observational study, with no other supporting evidence – the recommendations being fundamented on studies predating the reviewed period. The studies conducted during the reviewed period have not been able to confirm the efficacy of activated protein C.

In the reviewed period (2004-2009) there have been no contributions with sufficient evidence to allow new or further recommendations. Although lacking the abundant body of evidence obtained for other therapeutic measures, inhalatory nitric oxide, the statins and immunoglobulins are probably good alternatives in the adjuvant treatment of sepsis.

We will have to wait for the results of the different clinical trials on the new therapies in sepsis, which are presently in course. The future possibly may lie in stem cells and gene therapy.

Conflict of interest

The authors declare no conflict of interest.

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