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ADVANCES IN SEPSIS

Commentary and analysis on advances in the understanding and treatment of sepsis

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Dear Colleague

Welcome again to *Advances in Sepsis*.

In the first article of this issue, Professor Benoît Vallet and colleagues (University Hospital of Lille, Lille, France) provide a thorough review of the management of patients with septic shock, in terms of titration of vasopressors and appropriate fluid loading. The authors initially describe the complexities associated with an accurate diagnosis of shock, then discuss the observations and interventions required during the initial management of these subjects. The role of fluid and vasopressor therapies is described, and optimal titration of these interventions is discussed. Lastly, the authors propose a protocol for the weaning of patients from vasopressors.

Professor Giorgio Berlot and colleagues (University of Trieste, Trieste, Italy) present an excellent review of the use of intravenous immunoglobulins (IvIg) in sepsis. Although there is a paucity of evidence from large, randomized controlled trials for the use of IvIg in sepsis, the effects of immunoglobulins on the inflammatory response is well documented, and there are reports describing beneficial effects of IvIg in subgroups of patients, including pediatric sepsis patients. Professor Berlot and colleagues describe the potential modes of action of IvIg in attenuation of the inflammatory response in sepsis, and subsequently discuss the rationale for and clinical uses of IvIg in sepsis.

In the third leading article of this issue, Dr Catherine Bouman (University of Amsterdam, Amsterdam, The Netherlands) examines the application of high-volume hemofiltration (HV-HF) as an adjunctive therapy in sepsis. Dr Bouman presents an overview of the principles of hemofiltration and hypotheses for the mechanisms of action of the procedure. Preclinical and clinical studies of the use of HV-HF are discussed, and are succinctly illustrated in tables.

In the Surviving Sepsis section of this issue, the progress of the Surviving Sepsis Campaign's data collection database is reported. Publication of the upcoming Surviving Sepsis Campaign guidelines revision, which will further the Campaign's goals, is keenly awaited. As in all issues, the Clinical Reviews provide concise and critical analyses of the latest and most important sepsis literature, placing recent developments in a clinical context. Lastly, Dr Timothy Girard (Vanderbilt University School of Medicine, Nashville, TN, USA) presents an overview of the most outstanding sepsis-related presentations from the 36th Critical Care Congress of the Society of Critical Care Medicine, held earlier this year in Orlando, FL, USA.

We would like to thank all those readers who have taken time to provide feedback on the articles presented in *Advances in Sepsis*. We are pleased that the comments have been overwhelmingly positive and that the journal continues to be regarded as a useful resource by clinicians working in this fast-developing field.

Benoît Vallet and Mitchell M Levy

Editors-in-Chief

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Aims and Scope
Advances in Sepsis is designed to bring a critical analysis of the recent world sepsis literature, written by clinicians, for clinicians, to an international, multidisciplinary audience. Our mission is to promote better understanding and treatment of severe sepsis and septic shock across the global healthcare system by providing an active forum for the discussion of clinical and healthcare policy issues.
Leading Articles – These major review articles are chosen to reflect topical clinical and healthcare policy issues in sepsis care. All contributions undergo a strict editorial review process.
Surviving Sepsis Campaign: Quarterly Update – Each issue of *Advances in Sepsis* contains a specially commissioned article on implementing the Surviving Sepsis Guidelines and an update on the progress of the Campaign.
Clinical Reviews – The most important papers from the international literature on sepsis are systematically selected by an internationally recognized panel of experts. The Editors then prepare concise and critical analyses of each paper, and, most importantly, place the findings into clinical context.
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Commonwealth House, 1 New Oxford Street, London WC1A 1NU, UK.
Telephone: +44 (0)20 7759 2999 Fax: +44 (0)20 7759 2951 Email: info@advancesinsepsis.com

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LEADING ARTICLE

How to Titrate Vasopressors Against Fluid Loading in Septic Shock

Benoît Vallet, MD, Hervé Tytgat, MD, and Gilles Lebuffe, MD

Department of Anaesthesiology and Intensive Care Medicine, University Hospital of Lille, Lille, France

The initial management of patients with septic shock includes ensuring oxygen supply, fluid therapy, consideration of inotrope or vasopressor therapy, and specific treatments to address the cause. The assessment and treatment of septic shock is confounded by the fact that shock may be present with a normal blood pressure, and patients in septic shock may present with a high or low cardiac output (CO), and a variable amount of intravascular volume depletion. Thus, vasopressors and fluid loading should be used to maintain tissue perfusion, rather than maintaining blood pressure. This review describes the assessment of circulatory function and initial management of patients with septic shock, and specifically details the process of titrating vasopressors against fluid loading in septic shock. The appropriate weaning of patients from vasopressors is also discussed. The authors present several arguments for the monitoring of CO in order to facilitate the best course of treatment in septic shock patients. *Adv Sepsis* 2007;**6**(2):34–40.

In clinical practice, the terms "hypotension" and "shock" are often used interchangeably. However, it is important to stress that shock may be present despite a normal blood pressure. Correspondingly, blood pressure may be low without shock being present. Hypotension can be defined as a drop in systolic blood pressure of >40–50 mmHg from baseline, a systolic value of <90 mmHg, or a mean arterial pressure (MAP) of <65 mmHg. Hypotension can result from either a low cardiac output (CO) and/or a low systemic vascular resistance (SVR) because MAP is determined by both CO and SVR (MAP = CO × SVR). Hypotension does not necessarily equate to shock but, in the critically ill patient, is often associated with a reduction in the level of oxygen transport (TO_2) to tissues or its utilization therein. A low CO is likely to be associated with a low TO_2 (TO_2 = CO × CaO_2, where CaO_2 is arterial oxygen content). When TO_2 decreases, ventilatory oxygen consumption (VO_2) is maintained (at least initially) by an increase in oxygen extraction (EO_2). Increased EO_2 is consistent with adapted vascular reactivity, increased SVR, and redistribution of blood flow. In contrast, low vascular resistance is often associated with impaired EO_2 by tissues; this may be associated with mitochondrial pathology. When TO_2 decreases beyond a certain threshold it induces a decrease in VO_2. This point is known as the critical TO_2 (TO_2crit), below which there is a state of oxygen uptake-to-supply dependency (shock or dysoxia). TO_2crit is higher when EO_2 is lower. Below the TO_2crit, a decrease in VO_2 is associated with an increase in lactic acid production and an inadequate supply of adenosine triphosphate (ATP) relative to cellular requirements. In sepsis, as in carbon monoxide or cyanide poisoning, dysoxia may also occur as a consequence of mitochondrial damage or inhibition where oxygen is available, but not consumed [1].

In the clinical setting, the mixed venous oxygen saturation (SvO_2) can be used to assess the whole body VO_2–TO_2 relationship. In the absence of a pulmonary artery (Swan–Ganz) catheter (PAC), the central venous oxygen saturation ($ScvO_2$) is being increasingly used as a reasonably accurate surrogate. Tissue VO_2 can be calculated according to the Fick equation: $VO_2 \approx CO \times (SaO_2 - SvO_2) \times Hb \times 1.34$, where SaO_2 represents arterial oxygen saturation and Hb represents hemoglobin; SvO_2 can be derived using the calculation: $SvO_2 \approx SaO_2 - VO_2 / (Hb \times 1.34 \times CO)$.

Cardiogenic, hypovolemic, and obstructive etiologies are generally associated with low-CO states and have corresponding clinical features. The circulation of a patient who has hypotension with a septic cause is usually hyperdynamic. However, profound myocardial depression (from excess nitric oxide production and release of myocardial depressant factors), major third space fluid losses (capillary leak, with additional fluid and electrolyte depletion from a variety of routes, e.g. sweat, vomit, diarrhea), and/or extreme vasodilatation (due to excessive activation of macrophages, neutrophils, or endothelium and over-production of pro-inflammatory mediators such as prostanoids, nitric oxide,

Address for correspondence: Benoît Vallet, Pôle d'Anesthésie & Réanimation, Hôpital Huriez – CHRU de Lille, Rue Michel Polonovski, F59037 Lille cédex, France. Email: bvallet@chru-lille.fr

kinins, and pyrogens) may produce a low-flow state. Vascular hyporeactivity is related to decreased responsiveness to catecholamines and variable degrees of endocrine dysfunction (notably adrenocortical). Thus, patients in septic shock may present with a high or low CO, and a variable amount of intravascular volume depletion [1].

Initial management of septic shock

Owing to the lack of specificity of key clinical features in the classification of hypotension, diagnosis and treatment should be considered simultaneously since a good response to treatment helps to confirm the working diagnosis. Immediate management includes ensuring oxygen supply, fluid therapy, assessment of the need for inotrope or vasopressor therapy, and consideration of specific treatments to deal with the direct cause.

Proposed monitoring

In life-threatening situations, empirical treatment should not be delayed while monitoring devices are being inserted. Basic cardiorespiratory monitoring comprises measurement of heart rate and blood pressure, and pulse oximetry. Arterial blood pressure should be recorded at a minimum of 5-min intervals but ideally it should be monitored continuously, and whenever possible invasively, in the unstable patient [2]. Noninvasive measurements are often unreliable in shock states, and invasive arterial pressure monitoring should be instituted as soon as possible.

Central venous catheter

A central venous catheter allows measurement of central venous pressure (CVP). A static measurement of CVP is not particularly useful in deciding the need for fluid administration, although it is generally indicative when the pressure is <5 mmHg. The response of CVP to a fluid bolus is more useful (as is discussed below). The central venous catheter also allows monitoring and/or sampling of blood for measurement of $ScvO_2$ (the surrogate for mixed SvO_2), depending on whether or not an oximetry catheter is being used. A central venous catheter is simpler to insert, and generally safer and cheaper than a PAC.

The four determinants responsible, either alone or in combination, for a decrease in SvO_2 (or $ScvO_2$) are: hypoxemia (decrease in SaO_2), an increase in VO_2 without an increase in TO_2, a fall in CO, and a decrease in Hb level. The normal range for SvO_2 is 68–77% (+5% for $ScvO_2$). An increase in VO_2 without an increase in CO or TO_2, or a decrease in TO_2 and no change in oxygen requirements, will result in an increase in EO_2 and a fall in SvO_2. EO_2 and SvO_2 are linked by a simple equation: $EO_2 \approx 1 - SvO_2$, assuming $SaO_2 = 1$ [3].

Tissue dysoxia is usually present when SvO_2 falls below 40–50%; however, this may also occur at higher levels of SvO_2, when EO_2 is impaired. Therefore, other markers of cellular O_2 inadequacy should be sought, such as hyperlactatemia. Usually, efforts to correct CO (fluids or inotropes), Hb level, SaO_2, VO_2, or a combination of the parameters must target a return of SvO_2 ($ScvO_2$) from 50% to 65–70% [2].

CO monitoring

A PAC, which may be equipped with continuous CO- and SvO_2-monitoring modalities, and/or any less invasive flow assessment technique (e.g. transesophageal echocardiogram, esophageal Doppler, LiCO, or peripheral transpulmonary dilution) is recommended when hypotension persists or a precise CO optimization is required (e.g. for fluid loading). Fluid challenges should be repeated until the top of the Frank–Starling curve is reached – that is, when stroke volume does not increase >10% following a 250-mL colloid challenge. At this point, the ventricle becomes preload-independent [4].

Echocardiography

Echocardiography may provide a rapid insight into the differential diagnosis, particularly when the true problem is unclear. For example, in the context of congestive heart failure, myocardial ischemia, or sudden collapse, it may diagnose any potentially reversible ventricular, valvular, or obstructive pathology. It provides information on both left and right ventricular function and can provide an initial assessment of preload and the presence of any regional wall-motion abnormalities. Echocardiography should not be considered simply within the context of CO assessment, but within the context of global cardiac performance, which can be altered in sepsis [5]. However, it is possible that bedside bidimensional echocardiography is still not available in all general intensive care units (ICUs).

Systolic pressure, pulse pressure, and stroke volume variations

In the sedated, intubated, and ventilated patient, recordings of systolic pressure variation (SPV), pulse pressure variation (ΔPP), stroke volume variation (SVV), or a combination of these can be helpful in the absence of flow-monitoring technology; the left ventricle remains preload-dependent until the SPV is <10 mmHg (SVV variation threshold of 10%), ΔPP is <13%, or SVV is <10%. Unfortunately, arrhythmias or spontaneous breathing preclude this type of evaluation [6].

Tissue perfusion indices

Interference of sepsis-modified vasoactive drug properties by sepsis-induced microcirculatory disturbances has

predominantly been investigated at the level of the splanchnic circulation using techniques such as regional capnometry, laser Doppler flowmetry, and indocyanine green dilution. Besides measurement of lactate concentration, determination of gastric tonometered-to-arterial carbon dioxide pressure (PCO_2) remains the unique clinical monitoring tool that can aid in the assessment of the efficacy of fluid loading or catecholamine infusion on tissue perfusion [7]. The venous-to-arterial carbon dioxide difference can, to some extent, be proposed as a surrogate for tissue perfusion assessment, as suggested by Mekontso-Dessap et al. [8].

Fluid therapy

With the possible exceptions of severe heart failure and pericardial tamponade, the vast majority of hypotensive septic patients require fluid as first-line therapy because hypovolemia is nearly always present. Hypovolemia can be either absolute or relative. Absolute hypovolemia is observed with loss of intravascular fluid externally (gut or renal losses, or hyperthermia) or into extravascular compartments (capillary hyperpermeability). Relative hypovolemia is observed as a result of decreased vascular tone, resulting in an increase in the total intravascular compartment size.

The response to initial treatment dictates further management. In situations where volume loss is likely, immediate fluid resuscitation should be started before further investigations are carried out.

Fluid therapy maintains a preload level necessary to support CO and systemic TO_2. Crystalloids, colloids, blood or blood products, or a combination of these is used for this purpose. Although experts argue over the advantages and disadvantages of particular colloid or crystalloid solutions, there is consensus on the need to administer enough fluid to restore an adequate circulation [9].

Vasopressor therapy

An inotrope and/or mechanical support should be considered if an inadequate MAP persists with signs suggestive of organ hypoperfusion, such as oliguria, altered conscious state, chest pain, cardioscope changes, low SvO_2 (or $ScvO_2$), elevated lactate concentration, or arterial base deficit. After adequately restoring intravascular fluid volume, persistent hypotension requires the use of drugs that either improve myocardial contractility (to increase CO) and/or increase vascular tone (to increase SVR).

Owing to their short half-life (minutes) and familiarity with their use, catecholamines are usually the preferred first-line agents. Taking into account their effects on cardiac contractility (inotropism) and vascular tone (constrictor or dilator effects), they can be separated into two major classes: inodilators (inotrope plus vasodilator: low-dose dopamine and any dose of dobutamine or dopexamine), or inoconstrictors (inotrope plus vasoconstrictor: high dose dopamine, any dose of norepinephrine, and moderate-to-high doses of epinephrine).

Inodilators increase blood flow, but may actually have excessive vasodilating effects; inoconstrictors or vasopressors increase perfusion pressure and have variable effects on flow. The detection of a marked decrease in left ventricular ejection fraction using echocardiography can suggest the use of dobutamine when signs of peripheral hypoperfusion persist, despite volume resuscitation and restoration of perfusion pressure with vasopressors.

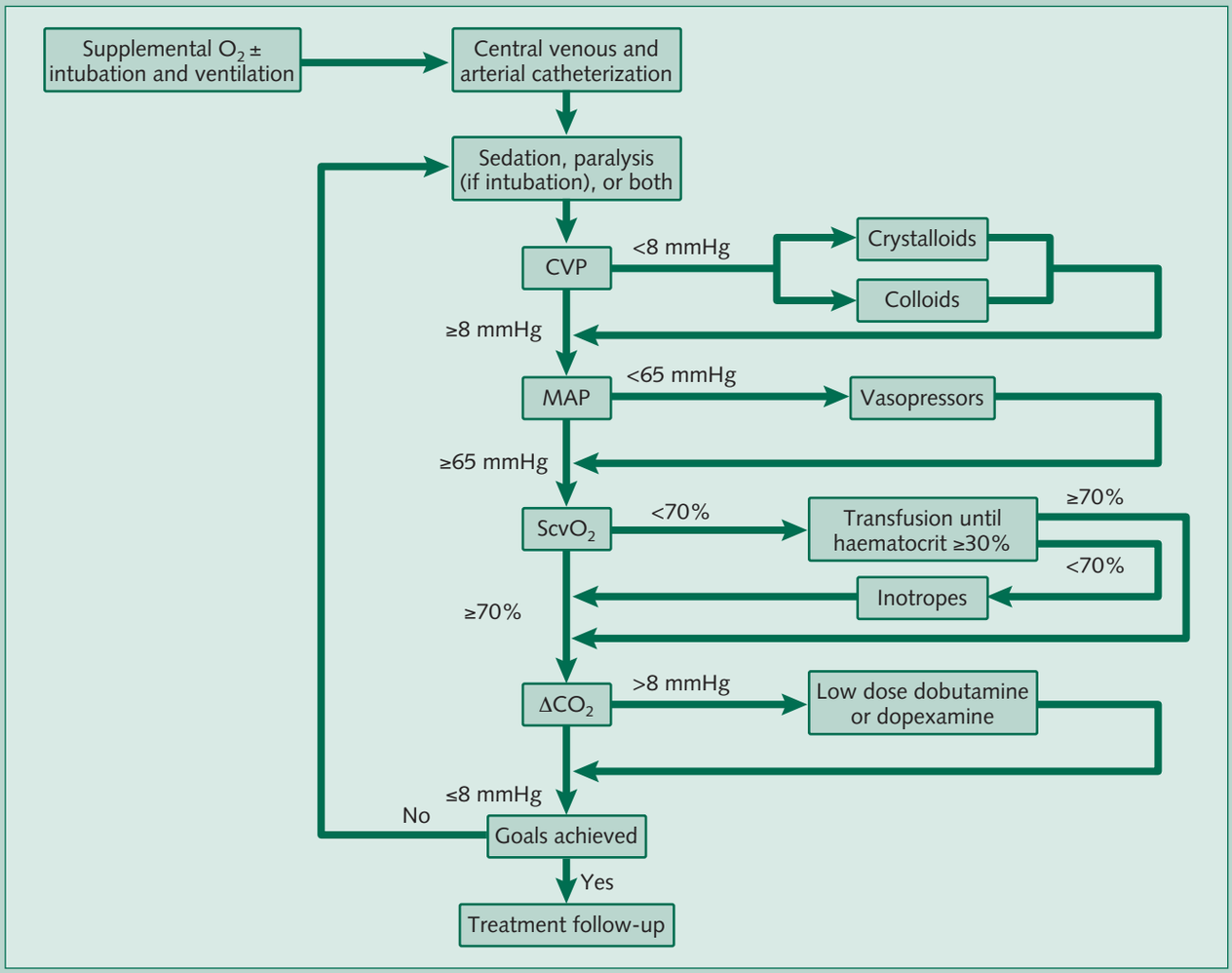
Because of a highly variable individual sensitivity to these different catecholamine agents, dose titration is strongly recommended, ideally against measurement of CO as well as blood pressure and other relevant variables such as base deficit and urine output. Non-catecholamine vasopressors such as vasopressin and its synthetic analogue terlipressin are now being evaluated in sepsis and other vasodilatory shock states. As increasing blood pressure through vaso-constriction is often associated with a decrease in CO, a trade-off is necessary between raising blood pressure and decreasing CO. This will dictate the choice and dosage of vasopressor and/or vasoconstrictor, as no purely inotropic agents exist.

The Surviving Sepsis Campaign (SSC) recommends maintaining MAP at ≥65 mmHg in septic shock patients [9]. It is important to emphasize that an increase in blood pressure may not be a good surrogate of clinical benefit. Indeed, in a large, placebo-controlled clinical trial, administration of the non-selective nitric oxide inhibitor *N*G-methyl-L-arginine in septic shock produced significant increases in both blood pressure and mortality rate [10]. Thus, the aim should be to improve tissue perfusion and not simply to increase blood pressure.

How to titrate fluid loading and vasopressor

The risk, when using vasopressors, is to inadequately fluid-load patients and to decrease tissue perfusion. Preload assessment in the context of increased vascular tone and vasopressor-induced reduced vascular compliance does not predict tissue perfusion. In a recent experimental study, Nouira et al. clearly demonstrated that preload independency could be artificially created by infusing norepinephrine following hemorrhagic shock [11]. In hemorrhaged dogs (in which 35 mL/kg of blood was withdrawn), norepinephrine, in the absence of fluid or red blood cell infusion, resulted in a return of ΔPP from 28% to a normal 12%, while MAP and CO were increased from 85 to 153 mmHg and from 1.98 to 3.08 L/min, respectively.

Figure 1. Proposed modified protocol for early goal-directed therapy.

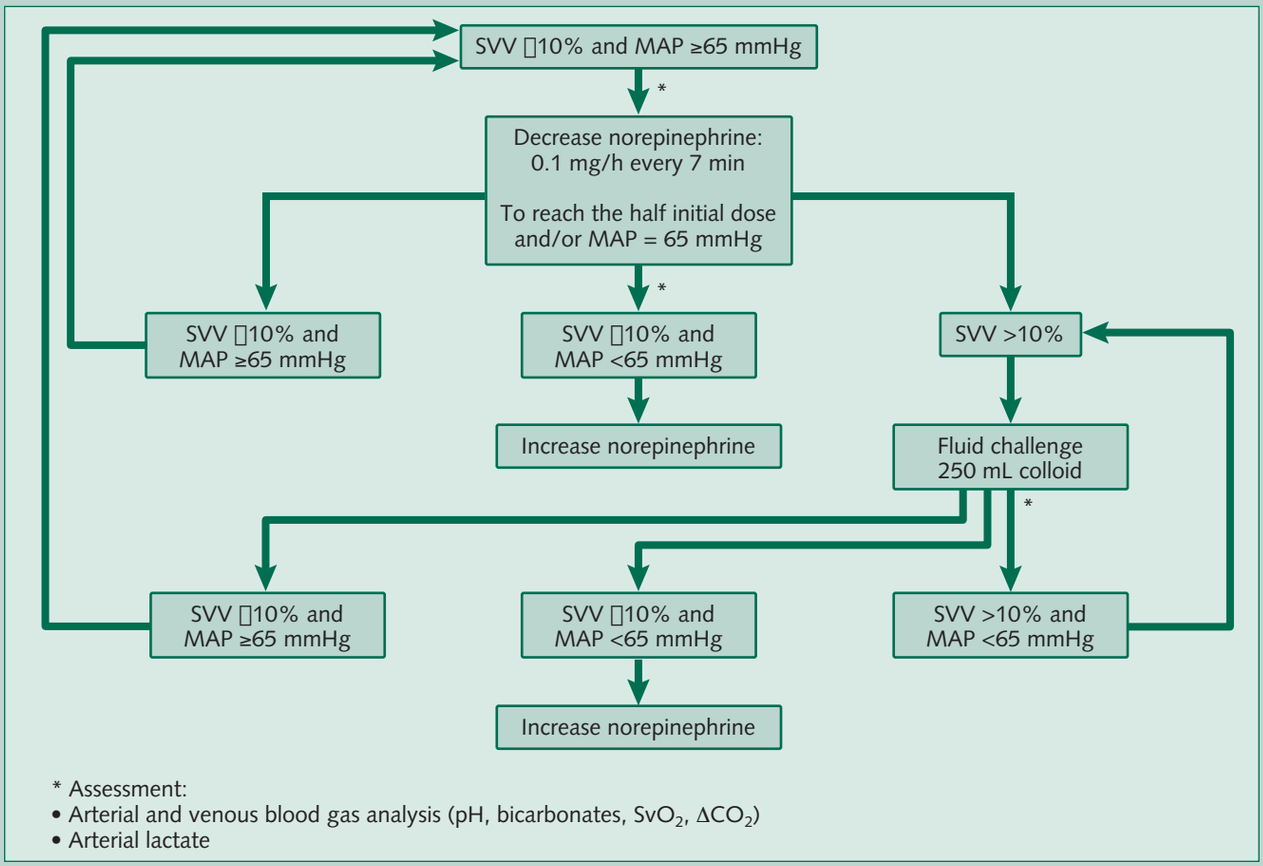


CVP: central venous pressure; ΔCO_2: venous-to-arterial or gastric-to-arterial carbon dioxide difference; MAP: mean arterial pressure; $ScvO_2$: central venous oxygen saturation. Redrawn with permission from Rivers et al. [12]; Copyright © 2007 Massachusetts Medical Society. All rights reserved.

Conversely, despite normalization of hemodynamics, pH and bicarbonates fell from 7.29 to 7.24 and from 18.0 to 15.8 mmol/L, respectively. These data clearly show that oxygen-derived parameters need to be taken into account when vasopressors are used in shock states in order to accurately titrate the drugs against fluid loading.

In a landmark study by Rivers et al. [12], patients admitted to an emergency department with severe sepsis and septic shock were randomized to standard therapy (aiming for a CVP of 8–12 mmHg, MAP ≥65 mmHg, and urine output ≥0.5 mL/kg/h), or to early goal-directed therapy (EGDT) where, in addition to the previous parameters, an $ScvO_2$ of ≥70% was targeted by optimizing fluid administration, keeping hematocrit ≥30%, and/or giving dobutamine to a maximum of 20 μg/kg/min (Fig. 1). The initial $ScvO_2$ in both groups was low (49±12%), which serves as a reminder that severe sepsis is often a hypodynamic condition before fluid resuscitation is started. From the first to the 72nd hour, the total fluid loading was not different between the two groups (≈13.4 L); in contrast, from the first to the seventh hour the amount of fluid received was significantly greater in the EGDT patients (≈5000 mL vs. 3500 mL). Conversely, from the first to the 72nd hour, the number of patients treated by vasopressor was significantly lower in the EGDT group (36.8% vs. 51.3%; p=0.02). This was also the case from the first to the seventh hour although this was not a significant difference (27.4% vs. 30.3%; p=0.62). In the follow-up period between the seventh and the 72nd hour, mean $ScvO_2$ was higher (70.6±10.7% vs. 65.3±11.4%; p=0.02), as was mean arterial pH (7.40±0.12 vs. 7.36±0.12; p=0.02) in patients receiving EGDT. Lactate plasma levels were lower in those receiving EGDT

Figure 2. Tentative protocol for vasopressor withdrawal.



ΔCO_2: venous-to-arterial carbon dioxide difference; MAP: mean arterial pressure; SVV: stroke volume variation; SvO_2: venous oxygen saturation.

(3.0±4.4 mmol/L vs. 3.9±4.4 mmol/L; p=0.02), as was base excess (2.0±6.6 mmol/L vs. 5.1±6.7 mmol/L; p=0.02). Organ failure score was also significantly altered in patients receiving standard therapy when compared with patients receiving EGDT. Hospital mortality rates fell from 46.5% (standard group) to 30.5% in the EGDT group (p=0.009). Importantly, 99.2% of patients receiving EGDT achieved their hemodynamic goals within the first 6 h compared with 86% in the standard group. This was the first study demonstrating that early identification of patients with sepsis plus initiation of EGDT to achieve an adequate level of tissue oxygenation by oxygen delivery (as judged by $ScvO_2$ monitoring) significantly improves mortality rates. Vasopressor titration in EGDT patients combined with MAP measurement and $ScvO_2$ assessment helped in reducing vasopressor therapy and to increase fluid loading when compared with a more conventional approach. This was followed by a net improvement in organ failure and mortality rate. In two recent successful trials in sepsis (using activated protein C or corticoids), a more rapid decrease in vasopressor therapy was observed together with an improvement in mortality rates, suggesting that if vasopressors need to be rapidly introduced in the initial therapeutic strategy, their benefit must then be frequently challenged, and the weaning process must be rapidly considered [13,14].

In ICU-resuscitated patients, SvO_2 or $ScvO_2$ may not be of help to guide titration of fluid loading and vasopressor therapy. The lower sensitivity of $ScvO_2$ in ICU stabilized patients may be that the severity of hypovolemia/myocardial dysfunction is usually lower at that stage. This might also be due to EO_2 defects related to severe microcirculatory disorders, or to mitochondrial damage and/or inhibition. In that context, measurement of SvO_2 or $ScvO_2$ would be expected to be elevated and one could suggest using the lactate and/or the venous-to-arterial PCO_2 difference to guide fluid loading toward perfusion-derived parameters [8].

To enhance the benefit in mortality rate reduction observed in EGDT patients, adding gastric-to-arterial carbon dioxide or venous-to-arterial carbon dioxide (ΔCO_2) assessment to refine

the Rivers et al. goal-directed protocol might therefore be useful (Fig. 1), although this has not yet been validated in formal studies. In order to decrease ΔCO_2 to ≤8 mmHg, several authors have suggested specific treatments aimed at improving tissue perfusion. This can be achieved using either low-dose dobutamine or dopexamine [15], or even by administering drotrecogin alfa (activated) [16].

Weaning process for vasopressor therapy

Removal of catecholamines is associated with the risk of inducing relative hypovolemia and preload dependency. Mallat et al. elegantly demonstrated that the decrease in catecholamine concentration during pheochromocytoma resection was associated with large SPV, which was significantly reduced by fluid loading [17]. However, the authors did suggest that catecholamine infusion needed to be considered when the fluid loading that was titrated to reduce SPV was not sufficient to correct MAP.

Similarly, the current authors hypothesize that lowering the dose of a vasopressor such as norepinephrine could unmask preload dependency, and that a protocol based on MAP and SPV, ΔPP, or SVV should be considered (Fig. 2). This protocol could help in safely reducing norepinephrine dose; moreover, the authors suggest that it might be associated with improved organ perfusion and more rapid vasopressor withdrawal. Biological parameters of organ perfusion should be assessed during the process (arterial and central venous blood gas analysis, with a special emphasis on SvO_2, pH and bicarbonate, and arterial lactate) in order to ascertain that the weaning process is not deleterious. Some safety limit to fluids, especially if SVV remains >10% and MAP at <65 mmHg, may be proposed, such as maintenance of CVP ≥12 mmHg.

Alternatively, stress-dose ("low dose") steroid therapy (50 mg hydrocortisone administered every 6 h) should be considered if maintenance of blood pressure levels requires increasing concentrations of vasopressors. Although the adrenocorticotropic hormone (ACTH) stimulation test has now been challenged, intravenous hydrocortisone is proposed to be administered after an ACTH test has been performed. If the clinical response is a decrease in the required vasopressor therapy together with a low baseline cortisol level and/or a subnormal response to ACTH (change in plasma cortisol level of <250 nmol/L) the corticosteroid should be continued. The duration of treatment should be 7 days, with a subsequent tapering off the drug for a further 5–7 days [16].

Conclusion

When aiming to titrate vasopressor and fluid loading in septic shock, the choice of monitoring technique to be used depends on familiarity with and availability of the procedure, the presence of exclusion criteria (e.g. dilution techniques are inaccurate in cases of moderate-to-severe tricuspid regurgitation), and potential risks (e.g. bleeding from line insertion in patients with concurrent coagulopathy). As discussed in this review, there are several arguments for monitoring CO in order to optimally titrate vasopressors and fluid loading. These are summarized here:

- Shock (dysoxia) may be present despite a normal blood pressure.
- It is easier to optimize fluid status and stroke volume in terms of constructing a Frank–Starling curve, especially with concurrent use of norepinephrine and poorly compliant lungs requiring high ventilator pressures and high positive end-expiratory pressure. This may enable earlier reduction/discontinuation of inotrope.
- In patients with critically low tissue TO_2 and supply–demand dependency with limited reserve to cope with further deterioration, CO monitoring facilitates the correct choice of treatment (including blood products, volume maintenance, and use of inotropes) and avoidance/early recognition of inappropriate and/or harmful therapies (and doses).
- An overall lack of outcome benefit may not necessarily apply to an individual case, especially in a severely ill individual.
- The pulmonary artery catheter allows assessment of preload dependency, CO, and pulmonary pressures in selected patients with severe lung injury. Continuous (or intermittent) monitoring of SvO_2 may be used to titrate therapy to improve oxygen supply–demand balance, for example, aiming for a mixed SvO_2 value >65–70%. Alternatives include echocardiography, esophageal Doppler, peripheral dye dilution or thermodilution techniques, and pulse contour analysis. $ScvO_2$ monitoring (intermittent or continuous) can be used as a surrogate for mixed SvO_2.
- Combined CO and MAP measurement together with preload dependency and SvO_2 ($ScvO_2$) assessment can help in appropriately titrating vasopressor therapy and fluid loading.

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LEADING ARTICLE

Immunoglobulins in Sepsis

Giorgio Berlot, MD, Barbara Bacer, MD, Marco Piva, MD, Umberto Lucangelo, MD, and Marino Viviani, MD

University of Trieste, Trieste, Italy

Polyclonal intravenous immunoglobulins (IvIgs) are frequently used in critically ill septic patients even though the clinical studies demonstrating their efficacy and safety are relatively small when compared with those performed using other drugs. There are several positive meta-analyses showing that the administration of IvIg in adult patients is associated with a reduced mortality rate; however, current guidelines for the treatment of sepsis largely restrict their use to neonatal sepsis. The authors review the basic mechanisms of action of IvIg, the rationale for their use, and their clinical applications. Similar to other therapeutic interventions in sepsis, it appears that the appropriate timing of administration represents a key factor to maximizing their beneficial effect. *Adv Sepsis* 2007;**6**(2):41–6.

Intravenous immunoglobulins (IvIgs) are approved by the US Food and Drug Administration for use in six conditions, but they are often prescribed off-label even in the absence of specific guidance formulated according to evidence-based medicine (EBM) criteria [1]. Among patients admitted to the intensive care unit (ICU), IvIg may be used either to boost the patients' immunological capabilities or to blunt an autoimmune response (for example, in myasthenia gravis or Guillan-Barré syndrome). These apparently opposing indications are a result of their pleiotropic effects on the immune system, which include the augmentation of the immune response through an increase of opsonization and phagocytosis, and activation of the complement system (discussed below); and also the downregulation of the inflammatory response via the reduced production of tumor necrosis factor-α (TNF-α) and other inflammatory mediators, and the increased release of soluble receptors for a number of cytokines [2,3]. The latter IvIg-mediated effects on the inflammatory response suggest that they may be suitable for the treatment of sepsis, which has been steadily increasing since the 1970s and is associated with a substantial mortality rate [4,5]. On the basis of several randomized, controlled clinical trials (RCTs), guidelines for the treatment of sepsis and sepsis-related complications have been proposed [6]. These criteria can be broadly divided into general supportive measures including the prompt administration of antibiotics, early aggressive cardiovascular support, and the lung-protective mechanical ventilation, and more specific guidelines, primarily targeted at the sepsis-induced pathophysiological derangements involving the coagulation cascade, the microvascular network, endocrine abnormalities, and the immunological response. The latter has been extensively studied since it became clear that the various biological manifestations of sepsis are primarily due to the interaction of the invading organism with the host [7,8], initially leading to a generalized inflammatory reaction, which eventually subsides to be replaced by a hyporesponsive state, concluding the clinical course [9]. An increasing number of mediators are involved in this two-step process; these are linked by a complicated array of positive and negative feedback loops [7–9].

On the basis of these considerations, it appears that the immunological treatment of septic patients may involve two distinct approaches. The first consists of the administration of IvIg to impede, or at least to blunt, the perpetuation of the initial response by attenuating the trigger substance(s). These Igs are directed primarily against antigens present on the surface of the infecting microorganisms, or towards factors that are released when the organism is killed by antibiotics, including endotoxin, peptidoglycans, and lipoteichoic acid. The second approach is based either on the direct inactivation of sepsis mediators that are produced and released in a more advanced phase of the inflammatory process, or on the neutralization of the receptors for these substances located on the cell surface. Despite sound pathophysiological and experimental bases for their use, the results of several RCTs aimed at investigating the clinical effects of the second approach have been largely below expectations and only a modest survival benefit, if any, was demonstrated in small groups of patients during *post hoc* analyses [10].

Address for correspondence: Giorgio Berlot, Department of Anaesthesia and Intensive Care, Ospedale di Cattinara, Strada di Fiume 447, 34100 Trieste, Italy. Email: berlot@inwind.it

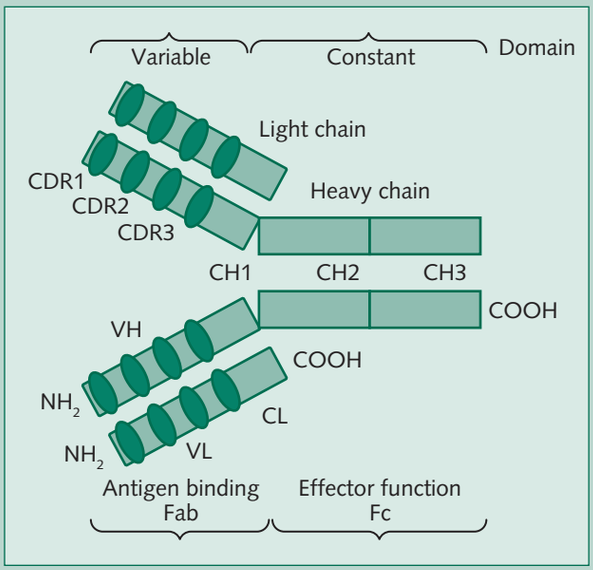
Structures and function of immunoglobulins

The ultimate mission of the immune system is to recognize and destroy extraneous molecules invading the host. To be inactivated, a foreign substance must react with fixed or circulating receptors, which trigger the final response. This task is accomplished by two distinct but strictly co-operating systems [8,11]. The innate immune system includes cells of reticuloendothelial system (RES) and the complement cascade. The number of receptors present on the surface of innate immune system cells is genetically determined and, albeit sufficient in number, cannot match the wide variability of microbial antigenic epitopes. Thus, a more flexible system is required in order to face the myriad of agents and/or substances that come into contact with the host. This second mechanism, known as adaptive immunity due to its capability to cope with continuously changing antigens, involves antibodies that are encoded by genes that are able to undergo somatic recombination and hypermutation. Antibodies are secreted by plasma cells, which are derived from B lymphocytes that are activated by trapping antigens on a cell-surface receptor and stimulation with $CD4^+$ T lymphocytes. Antibodies belong to five different classes of Ig (G, A, M, E, and D). The IgG class is considered the prototypical structure, and consists of a Y-shaped molecule comprised of two identical heavy (H) and light (L) peptide chains (Fig. 1). Both H and L chains are divided into a variable (V) domain that reacts with the antigen, and a constant (C) region that activates the various components of the innate immune system, triggering a response (for example, phagocytosis, antibody-mediated and cell-mediated cytotoxicity, and complement-mediated lysis). The region connecting the two functional parts can undergo conformational changes in order to re-shape the molecule according to the antigen variability. Therefore, Igs can be considered biochemical transducers that are able to:

- Recognize invading micro-organisms and derived substances.
- Opsonize bacteria.
- Signal their presence directly or via the complement cascade to the cells of innate immune system, which are ultimately responsible for their destruction.
- Neutralize bacteria-derived toxins [2,11].

Igs are widely used both as therapeutic and diagnostic tools in many fields of medicine. On the basis of their specificity, IvIg preparations can be grouped into monoclonal – containing a single class of Ig directed against a single epitope of those present upon a target molecule (e.g. one epitope of TNF-α), or polycloclonal – containing Ig directed against multiple epitopes of the target substance. The additional immunomodulatory effects attributed to the latter class are due to naturally occurring autoantibodies and some non-immune proteins present in the preparation [2].

Figure 1. Schematic two-dimensional structure of an IgG molecule. VH and VL indicate the variable regions of the heavy and light chains, respectively. The different epitopes are recognized by the variable regions located on both the light and heavy chains (Fab region). The CDR segments are hypervariable domains located in the Fab regions, which are separated from each other by relatively constant polypeptide chains. The Fc region binds to complement and to the receptors located on the surface of the RES cells and triggers their activation.



CDR: complementary determining region; COOH: carboxyl; C: constant; Fab: fragment antigen binding; Fc: fragment crystallizable region; H: heavy; IgG: immunoglobulin G; L: light; NH_2: amino; RES: reticuloendothelial system; V: variable.

Rationale for the use of IvIg in sepsis

Several lines of evidence support the use of IvIg in sepsis, including the increased clearance of endotoxin by the RES, the increased production of free radical species by macrophages and the enhancement of phagocytosis by neutrophils exposed to different Ig classes (G, M, and A) [12,13]. In septic patients, spontaneously elevated levels of IgM anti-endotoxin antibodies are associated with a better outcome [14], and this effect can be replicated by the administration of an IgM-enriched polyclonal IvIg preparation in patients [15]. It has also been demonstrated that IgM, and to a lesser extent IgG, can downregulate the activation of complement during inflammation (Table 1) [12]. Due to their mechanisms of action, IvIgs are used in clinical

Table 1. Possible mechanisms of action of immunoglobins [3,12].

Toxin inactivation
Neutralization of endotoxin and exotoxins
Increase clearance of endotoxin
Reduce bacterial cell adherence, invasion, and migration
Stimulation of the leukocyte and serum bactericidal action
Enhancement of endotoxin-induced neutrophilic oxidative burst (7S-IvIgG; intact IgG)
Reduction of endotoxin-induced neutrophilic oxidative burst (5S-IvIgG; F(ab')2 IgG fragments and IgM)
Enhancement of serum opsonic activity
Modulation of cytokine effect
Modulation of the release of cytokine and their antagonists
↓ Pro-inflammatory mediators
↑ Anti-inflammatory mediators
Infusion of cytokines and antagonists contained in the Ig preparations
Cytokine neutralization by anti-cytokine antibodies
Modulation of the complement cascade

IvIg: intravenous immunoglobulin.

practice with the dual aim of preventing the occurrence of a number of diseases by passively immunizing the subjects who are at risk, and of modulating the inflammatory reaction. Both monoclonal and polyclonal Ig preparations have been used in septic patients, with different results [3,12,13]. Indeed, the recent history of critical care medicine has been marked by a number of RCTs studying the effects of monoclonal IvIg targeted against endotoxin and several different sepsis mediators. However, despite the sound biological bases and the results of preliminary trials performed in small number of patients, the results of larger RCTs using these "magic bullets" did not confirm these premises, or even demonstrated a better outcome in the control arm [16]. Only *post hoc* analyses could identify, in some studies, small subsets of patients who benefited from this approach [10]. Various clinical reasons have been proposed as an explanation for these contradictory results, including the role of co-existing disease in determining the outcome, the choice of 28- or 56-day survival as the study endpoints, and the appropriateness of concomitant treatments [16]. Another possible reason may involve the treatment itself, and the rationale behind monoclonal Ig therapy. The production and release of sepsis mediators should be considered as a network rather than as a cascade; consequently, once the process is started, even if one of the substances responsible for the initial phase (i.e. TNF-α) is blocked, other mediators will likely maintain the septic response [17]. Put in teleological terms, the blockade of substances with immune capabilities that have been developed and conserved throughout evolution should not be considered completely safe, as demonstrated in studies in which the group receiving placebo had a better outcome [16–18]. Despite the disappointing results of trials, antibodies directed against some sepsis mediators are currently used to treat disorders such as Crohn's disease and rheumatoid arthritis, which, in contrast to sepsis, are characterized by a chronic and localized rather than acute and systemic inflammatory reaction [19]. However, the blockade *per se* of inflammatory mediators is not completely risk-free; in fact, the administration of anti-TNF-α antibodies in these clinical conditions has been associated with the occurrence of pulmonary and skin infections caused by intracellular agents, and the activation or reactivation of tuberculosis [20]. Thus at the present time, although novel molecules are still being produced and tested, the clinical use of monoclonal Ig directed towards some sepsis mediators is not supported by EBM criteria, and is limited to patients enrolled in RCTs.

Polyclonal preparations contain variable amounts of Ig directed against a variety of Gram-negative and Gram-positive epitopes and bacteria-derived substances, including endotoxin. In practical terms, several preparations containing predominantly IgG with only traces of other Ig are available (Polyglobin®, Bayer, Leverkusen, Germany) whereas only one product contains elevated concentrations of IgM (in addition to IgG) and minor amounts of IgA (Pentaglobin®, Biotest, Dreieich, Germany) Aside from the concentration of Ig, the various preparations also differ with regard to the stabilizers used [2]. Unlike monoclonal IvIg, polyclonal IvIgs are widely used in septic patients despite the lack of very large, positive RCTs. This popularity can be attributed to the widespread occurrence among critically ill patients of conditions associated with a downregulation of their immune capabilities, including postoperative status [21] and neoplasms [22]. Moreover, an ever-increasing number of subjects survive an initial insult and face a prolonged length of stay (LOS) in the ICU, which render them prone to repeated infections [23]. The extremely low incidence of severe side effects associated with their administration make them suitable in a wide range of clinical conditions [3]. However, it should be noted that, in most circumstances, it is difficult to separate true IvIg-related serious adverse events from complications of the underlying disease [24].

Clinical uses for IvIg in sepsis

Currently, it appears that polyclonal IvIg are used off-label either to prevent sepsis in at-risk subjects, or to treat existing sepsis and its consequences. However, in many cases, a clear-cut differentiation between the two situations is difficult to establish as the margin separating uncomplicated infection from sepsis is often ill-defined. To further complicate this issue – as often occurs in fields of critical care

medicine – clinical investigations frequently group patients with diverse underlying conditions.

Several investigators have studied the effects of prophylactic IvIg administration in different categories of patients who are prone to infections and sepsis, including premature infants and patients undergoing heart surgery. Premature infants are susceptible to sepsis due to a relative insufficiency of humoral immunity, primarily dependent on the reduction of the trans-placental passage of maternal Ig, which begins at 8–10 weeks of gestation and accelerates during the third trimester. A meta-analysis has addressed the effects of exogenous Ig administration on the occurrence of sepsis in premature infants and neonates, and a marginal reduction of early-onset neonatal sepsis has been demonstrated, primarily in premature newborns with a low birth weight [25]. When considering the cost of treatment, Jenson et al. concluded that the routine prophylactic administration of IvIg in premature neonates is not cost-effective and should not be recommended [25]; conversely, as their use is associated with a substantial reduction of the mortality rate associated with neonatal sepsis, they should be administered as a standard treatment in association with antibiotics in premature infants with sepsis [25,26]. This issue should continue to be considered as open, as other studies have failed to identify any survival benefit in neonatal sepsis [27].

In addition to premature infants, patients undergoing heart surgery are at an elevated risk of sepsis due to different causes, including the presence of multiple invasive devices and a prolonged ICU LOS; moreover, the use of cardio-pulmonary bypass (CPB) can trigger a systemic inflammatory reaction primarily ascribed to the interaction between the blood and the extracorporeal circuit and/or the absorption of endotoxin through the gut mucosa [28]. These effects appear decreased in patients undergoing off-pump procedures, which are increasingly used as they have been associated with fewer complications and reduced costs [29]. Due to the inflammatory effects associated with CPB, the administration of IvIg has been advocated for their immunomodulatory effects in patients undergoing heart surgery [28]. Several investigations demonstrated that the administration of either IgG- or IgM-enriched IvIg could reduce morbidity and the severity of disease in a group of postoperative heart surgery patients with an Acute Physiology and Chronic Health Evaluation (APACHE) score ≥24 at the first postoperative day after CPB [30–32]; another study that investigated the effects of IgM-enriched IvIg confirmed these results, and demonstrated that the beneficial effect was limited to more seriously ill patients who developed severe sepsis after heart surgery [33].

According to the current EBM-derived indications for the treatment of septic patients, it is suggested that the administration of polyclonal Ig should be limited to pediatric sepsis [6,34]. This statement is rather surprising since a previous meta-analysis based on the results of nine studies that included >400 patients with sepsis and septic shock demonstrated that the risk of mortality in patients given Ig was lower than that in control subjects (relative risk [RR] 0.60, 95% confidence interval [CI] 0.47–0.76) [35]. This beneficial effect was significant in adult (n=222; RR 0.60, 95% CI 0.47–0.77) but not in pediatric patients (n=191; RR 0.60, 95% CI 0.31–1.14). These results have been confirmed by a more recent meta-analysis including a much larger number of subjects, which demonstrated a better survival in adult septic patients given polyclonal IvIg compared with control subjects (n=2621; RR 0.74, 95% CI 0.62–0.89) [36].

The weakness of the investigations concerning the use of polyclonal IvIg in sepsis – and therefore of the derived meta-analysis – lies in the relatively small number of patients included, and the heterogeneity of their underlying conditions [37]. The difficulties encountered in defining the exact role of IvIg according to EBM criteria can be imagined if one considers that only 20 studies out of >4000 were considered eligible for systematic review by Turgeon et al. [36]. Apart from the effects on the survival, there is some evidence to suggest that polyclonal IvIg can reduce the occurrence of sepsis-related critical illness polyneuropathy (CIP), which has been associated with a difficult weaning from mechanical ventilation and a prolonged in-ICU and in-hospital LOS [38,39]. As different anatomical structures including the peripheral nerve, the neuromuscular plaque, and muscle participate in the pathogenesis of the CIP, it is not yet clear whether this beneficial effect can be ascribed to a better control of the septic process or to a downregulation of the inflammatory reaction at the level of the involved component(s). A beneficial effects of polyclonal IvIg has also been demonstrated in less frequently encountered critically ill patients who have toxic shock syndrome secondary to severe streptococcal group A infections [40,41]. With regard to the type of preparation of Ig, different meta-analyses have demonstrated an increased survival rate in patients treated with IgM-enriched IvIg compared with preparations containing IgG alone [42,43]. As the endotoxin molecule represents a target for IgM [14], this effect is particularly evident in patients who have Gram-negative infection [43].

There are a number of studies indicating that the administration of polyclonal IvIg is associated with either a reduced morbidity or an improved survival rate in different population of patients with sepsis, severe sepsis, and septic shock [44–47]. The improved survival rate is more marked in certain subsets of patients, such as those who have sepsis sustained by Gram-negative bacteria [3]. However, it is

Table 2. Comparison of some presently recommended treatment is septic patients [36,52,53].

Intervention	RR (95% CI)	NNT
Low tidal volume	0.78 (0.65–0.93)	11
Drotrecogin alfa (activated) (activated protein C)	0.80 (0.69–0.94)	16
Tight glycemic control	0.44 (0.36–0.81)	27
ICU LOS >5 days	0.52 (0.33–0.84)	10
Low-dose steroids	0.90 (0.74–1.09)	16
Non-responders	0.83 (0.66–1.04)	9
Selective digestive tract decontamination	0.65 (0.49–0.85)	12
Early goal-directed therapy	0.58 (0.38–0.87)	7
IvIg in adults	0.74 (0.62–0.89)	9

CI: confidence interval; ICU: intensive care unit; IvIg: intravenous immunoglobulin; LOS: length of stay; NNT: number needed to treat; RR: relative risk.

important to stress that IvIg should be considered as an adjunctive treatment that integrates with, but does not replace, appropriate antibiotic therapy, and may also be administered alongside the surgical drainage of the septic focus. This latter therapeutic approach could explain the contrasting results observed in different populations of patients; a number of RCT have actually demonstrated a more favorable outcome in surgical patients at risk of or with established sepsis who were given Ig, compared with control subjects [28,30,31,44–47], whereas the effects in medical patients, including those with malignancies and neutropenia, appears to be less straightforward [48,49]. Along with the source of sepsis, these results can be ascribed to a number of factors, including different time intervals elapsing from the diagnosis to the treatment, the exclusion of elderly patients, and the overall effect of comorbidities. In fact, the timing of administration appears to play a pivotal role, as demonstrated by Berlot et al., who observed that patients given IgM-enriched IvIg early in the course of severe sepsis had a significantly better survival rate than patients treated in a more advanced phase [50].

The overall costs of treatment represent another relevant issue in the treatment of sepsis patients. This topic has become particularly "hot" since an innovative and expensive molecule, drotrecogin alfa (activated) (recombinant human activated protein C [rhAPC], Xigris®, Eli Lilly and Company, Indianapolis IN, USA), was introduced into clinical practice following the publication of the results of a large RCT [51]. Recently, Neilson et al. [42] demonstrated, on the basis of a meta-analysis of several studies performed in adult sepsis patients treated with IgM-enriched IvIg, that the adjunct of this preparation to the standard therapy was associated with a reduced mortality rate, but did not decrease the ICU LOS. The addition of this preparation to the standard therapy implied an increase in expense of €5715–€28 443/life saved (LS) (approximately US$8050–US$40 000/LS). These figures incorporated the overall costs of a European ICU (including staffing, drugs, and blood products). Thus, the cost of IgM-enriched IvIg is not exceedingly elevated if one compares it with other interventions typical of an ICU setting, including the antibiotic treatment of abdominal infections with tazobactam/piperacillin or imipemen/cilastatin (€55 686/LS; approximately US$78 500/LS), or the administration of drotrecogin alfa (activated) (€100 728–€120 176/LS; approximately US$141 850–US$169 200/LS). Similar results have been confirmed by a separate meta-analysis [36], which demonstrated that IvIg compared favorably (and in some cases at a cheaper cost) with other measures currently recommended for the treatment of sepsis, both in terms of risk reduction and number of patients needed to treat to save one life (Table 2).

Conclusion

The treatment of sepsis is multifaceted and typically requires multidisciplinary competencies. In recent years, the immunological therapeutic approach has been extensively studied but the results of both experimental and clinical investigations have been puzzling, as the administration of monoclonal antibodies directed against specific sepsis mediators produced disappointing results, whereas the administration of the less specific IvIg was associated with better outcomes in different groups of patients. Despite these results, treatment with polyclonal IvIg is not recommended in current guidelines. On the basis of the published studies, it is possible to conclude that:

- Some categories of patients, including premature newborns of a low birth weight and patients undergoing heart surgery may benefit from the prophylactic administration of IvIg.

- Surgical patients treated with IvIg present a better outcome than control patients.
- The effect on medical patients is less clear, probably due to the presence of comorbidities that can influence the prognosis independently from the presence of sepsis.
- IgM-enriched IvIg preparations have been demonstrated to be more effective in reducing the mortality rate of patients with severe sepsis and septic shock than those containing predominantly IgG.
- Their efficacy is probably time-dependent, being maximal in the early phases of severe sepsis and/or septic shock.
- The costs compare favorably with other therapeutic interventions performed in septic patients.

To be definitively introduced into clinical practice and recommended by guidelines for the treatments of sepsis patients, a RCT is clearly required.

Disclosures

The authors have no relevant financial interests to disclose.

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LEADING ARTICLE

High-Volume Hemofiltration as Adjunctive Therapy for Sepsis and Systemic Inflammatory Response Syndrome: Background, Definition and a Descriptive Analysis of Animal and Human Studies

Catherine SC Bouman, MD, PhD

Department of Intensive Care, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

The application of high-volume hemofiltration (HV-HF) as adjunctive therapy in severe sepsis or systemic inflammatory response syndrome (SIRS) may improve outcome in critically ill patients, although this hypothesis remains a subject of significant debate. The original theory suggested beneficial effects of HV-HF through the removal of pro-inflammatory mediators. More recently, this theory was thought to be insufficient and novel hypotheses were proposed. Unfortunately, large, randomized controlled trials (RCTs) that are sufficiently powered for clinically meaningful outcomes are lacking. However, the effects of HV-HF in sepsis or SIRS have been studied in humans in small RCTs and observational studies, as well as in animal models. In humans, comparison among studies is hampered by the heterogeneity of both the study populations and hemofiltration strategies. Animal models overcome the problem of heterogeneity; however, they poorly mimic clinical practice. Of note, no two studies have applied the same definition for HV-HF. The present review discusses the new theories on HV-HF and its role as an adjunctive therapy in severe sepsis or SIRS, considering the literature over the last 15 years. In addition, the urge for a consensus definition for HV-HF is discussed, as well as the utility for future studies. *Adv Sepsis* 2007;**6**(2):47–57.

Continuous venovenous hemofiltration (CVVH) was originally designed as a substitute for lost renal function in critically ill patients with acute renal failure (ARF) [1]. In 1984, Gotloib et al. suggested additional beneficial effects of hemofiltration in septic lung injury resulting from the removal of inflammatory mediators [2]. This concept was reinforced by animal studies in the 1990s, in particular those in which very high ultrafiltrate rates were applied [3–5]. Notably, in these studies, the infusion of ultrafiltrate from septic donor animals into healthy acceptor animals resulted in decreased cardiac output and mean arterial pressure (MAP) [5,6], and death [4]. Studies in recent years have demonstrated that many soluble mediators of the systemic inflammatory (and anti-inflammatory) response syndrome (SIRS) can be removed by hemofiltration, although generally not resulting in decreased plasma levels [7]. Novel theories have been proposed in order to explain the beneficial effects of hemofiltration in the absence of an effect on mediator plasma levels [8–10]. The application of hemofiltration as adjunctive therapy in sepsis remains, however, a subject of debate [11].

Evaluation of the clinical efficacy of hemofiltration in sepsis is complicated by the heterogeneity of both the study populations and hemofiltration strategies. In addition to the role of hemofiltration, the outcome of sepsis is determined by many factors, including the virulence of the microorganism, polymorphism in cytokine genes of the patient, comorbidity, and concomitant treatment [12,13]. Experimental septic shock models overcome the problem of heterogeneity, although one should be careful when extrapolating the results of experimental shock to the clinical situation. The heterogeneity in hemofiltration operational characteristics further complicates evaluation of the role of

Address for correspondence: Catherine SC Bouman, Internist-intensivist, Department of Intensive Care, Academic Medical Center, University of Amsterdam, PO 22660, 1100 DD, Amsterdam, The Netherlands.
Email: c.s.bouman@amc.uva.nl

hemofiltration in sepsis. In particular, the question of treatment intensity has appropriately been raised.

The aim of the present review is to discuss the role of high-volume hemofiltation (HV-HF) in sepsis and SIRS, with specific consideration of the recent literature.

Principles of hemofiltration

In contrast to hemodialysis – removing substances by diffusion – clearance of solutes with hemofiltration is achieved by convection (ultrafiltration) and adsorption [14]. With the use of conventional membranes, convection is associated with greater removal of middle molecular weight substances – substances that play important roles in the pathogenesis of sepsis [15,16]. Both membrane (pore characteristics, pH, charge, and surface) and solute (geometry, charge, molecular weight, and protein binding) characteristics, and hemofiltration mode, determine the degree of removal by ultrafiltration and adsorption [17,18]. The ability of a solute to pass through a membrane is expressed by the sieving coefficient (ratio between the solute concentration in the ultrafiltrate and that in blood). For solutes freely crossing the membrane, sieving coefficients are equal or close to 1. The convective removal of a solute is the product of its sieving coefficient and the ultrafiltration rate, as long as the substitution fluid is administered after the filter (post-dilution). When the substitution fluid is delivered before the filter (pre-dilution), the convective clearance is decreased because of ultrafiltrate dilution [19].

Conventional membranes usually have a pore size of about 5 nm (*in vitro* cutoff 30–69 kDa). This allows for the removal of molecules up to a molecular weight of approximately 30 kDa. Although many mediators of sepsis have a molecular weight between 15 and 50 kDa, they are not freely filtered due to, for example, protein binding or trimer formation [20]. During *in vitro* hemofiltration, pre-dilution equals post-dilution regarding sieving coefficients for cytokines [17]. However, during *in vivo* hemofiltration there is normally clogging and protein cake formation, decreasing sieving coefficients for cytokines. Pre-dilution hemofiltration reduces protein cake formation. Therefore, there are some advantages to using pre-dilution to reduce protein cake formation (improving sieving coefficients), and also to the use of post-dilution (to increase convection). For some membranes, in particular the negatively charged polyacrylonitrile (AN69) membrane, adsorption is the main mechanism of mediator removal [21–24]. Nonetheless, adsorption to the membrane is subject to saturation of binding sites over time and secondary release from the membrane [17]. The blood–membrane interaction during hemofiltration can also induce the release of inflammatory mediators, although this process is much less frequent with the biocompatible membranes currently in use [25]. Thus, the net effect of hemofiltration on the circulating concentration of a mediator will depend on its volume of distribution, its sieving coefficient, the ultrafiltration rate and hemofiltration mode, its adsorption to the membrane, and its generation rate at tissue and membrane level.

Working mechanism of hemofiltration in sepsis: three theories

The original hypothesis suggesting beneficial effects of hemofiltration through the removal of pro-inflammatory mediators was thought to be insufficient and recently, three newer theories were put forward [8–10]. These three theories attempt to explain some of the beneficial effects of HV-HF in the absence of an effect on plasma levels of mediators.

The peak concentration hypothesis

This concept refers to the ability of hemofiltration to lower peaks in the blood compartment of both the pro- and anti-inflammatory mediators, reducing their toxic effects such as capillary leak, vasoplegia, and immunodepression. In this setting, higher ultrafiltration rates, promoting rapid and substantial removal of mediators, are privileged [10].

The threshold immunomodulation hypothesis

In this model, both mediators and pro-mediators are removed at the interstitial and tissue levels, secondary to removal from the blood compartment, to a point at which some pathways are completely shut down and cascades are blocked. At this threshold point, further tissue damage and organ injury is stopped in its tracks [9]. This theory might explain the clinical effects of hemofiltration when there is no change in blood compartment mediator concentrations. The mechanism by which ultrafiltrate intensity affects mediator flow from the interstitial to the blood compartment is unclear in this model. Furthermore, because cytokine and mediator levels do not decrease in the blood compartment despite significant changes at the tissue level and in the interstitium, it is difficult to determine when the threshold point has been reached.

The mediator delivery hypothesis

In this concept, HV-HF exerts its effect by re-invigorating lymphatic flow and function [8]. Crystalloid "replacement" solution of as much as 48–72 L/day is infused to restore intravascular volume lost through production of ultrafiltrate. Partial redistribution into the interstitium and lymph mobilizes inflammatory mediators and other proteins, cellular byproducts, excessive ground matrix, fragments of apoptotic cells, and free DNA. These substances are then

metabolized, scavenged, or cleared at multiple sites, including the reticuloendothelial system, liver, kidney, erythrocyte, and hemofilter.

Definition of HV-HF

It is rather inopportune that, in the literature, HV-HF applies to ultrafiltrate rates of 35–200 mL/kg/h and that a consensus definition for HV-HF is lacking. In a recent review on the effects of dose and timing of hemofiltration in sepsis and SIRS, hemofiltration dose was classified into low-volume (<30 mL/kg/h), high-volume (30–50 mL/kg/h), and very high-volume (>50 mL/kg/h) [26]. Similar definitions have been proposed by many experts in the field and have been presented at a number of congresses; however, the proposed definitions have never been discussed or validated during a "consensus conference". The duration of the technique should also be taken into account; there is a difference between pulse HV-HF and continuous HV-HF, for example. Thus, an index that considers dose and duration per day would be beneficial. Progress in the field of HV-HF is hampered by the absence of consensus definitions not only for the various forms of HV-HF, but for "timing" of hemofiltration as well [27]. In animal studies, hemofiltration is started far earlier than in clinical practice (Table 1), generally before or shortly after the septic insult. Moreover, no two human studies apply similar hemofiltration starting criteria. Recently, the Acute Kidney Injury Network proposed a consensus definition for acute kidney injury, and similar efforts should be made for defining the various HV-HF strategies, in addition to the timing of hemofiltration [28].

Studies on the effects of HV-HF in sepsis and SIRS

Characteristics of the studies evaluating the effects of (high-volume) hemofiltration are summarized in Table 1 (animal studies), Table 2 (randomized controlled trials [RCT] in humans), and Table 3 (observational studies in humans). In order to reflect the intensities of the hemofiltration treatments, both the ultrafiltrate rates as well as the durations are shown. Ultrafiltrate rate is expressed in mL/kg/h in order to facilitate comparison among studies. Bodyweight was estimated if not stated. Bodyweight for humans was estimated to be 75 kg in non-Asian countries and 55 kg in Asian countries. Studies from the last 15 years are shown in the tables. Animal and observational studies in humans that applied low ultrafiltration rates (<20 mL/kg/h) were discarded. In accordance with the recommendations of the Acute Dialysis Quality Initiative (ADQI) consensus statement, the effects of hemofiltration are classified into physiological and clinical endpoints [29]. Beneficial physiological endpoints include improved hemodynamic profile or decreased need for vasopressor drugs, improved vital signs, improved cardiopulmonary function, improved markers of renal function, or diminished microscopic organ damage. Beneficial clinical endpoints include organ dysfunction-free days, ventilator-free days, intensive care unit (ICU)-free days, duration of ICU/hospital treatment, dialysis-independent survival, cost-effectiveness analysis, survival to hospital discharge, relation between improved hemodynamic responses, survival rate, and immunological changes.

Animal studies

In animals, the negative studies are among those applying lower ultrafiltration rates (Table 1) [30–32]. An improved survival rate was reported in rats with endotoxin-induced shock after 4 h of hemofiltration (six out of six vs. none of six; $p<0.01$) [30]. However, this study did not include a nonfiltering control group, but compared hemofiltration to sham hemofiltration (hemofiltration with clamped ultrafiltrate line). Thus, the possibility that sham hemofiltration had negative effects (clamping of the ultrafiltrate allows the release of mediators due to the blood–membrane interaction while the convective removal of mediators is inhibited) cannot be excluded. A nonfiltering control group was included in the porcine endotoxin shock model of Murphey et al. and compared with hemofiltration and sham hemofiltration, but the differences in hemodynamic parameters were not statistically significant among the groups [31]. No beneficial effects following hemofiltration were shown in the recent study by Toft et al. in pigs with endotoxemia [32].

The most prominent effects in animal studies are observed when very high ultrafiltrate rates are applied both in blood-borne sepsis as well as in other, more compartmentalized forms of sepsis (Table 1). Beneficial effects were reported not only on hemodynamics and gas exchange [3–5,23,33–39], but also on sepsis-induced immunoparalysis [35,36], histological damage [33,38,39], and short-term survival rate [4,33,37,39]. In addition, the pancreatitis sepsis studies showed that HV-HF was more efficient than hemofiltration and low exchange rates [36–39].

Animal studies conducted to date, however, poorly mimic the clinical situation because hemofiltration was started before or very early after the insult, and because animals were not treated as "the state of the art" models regarding intensive care medicine at the time (e.g. inadequate volume loading, no antibiotics). The only negative HV-HF study was undertaken in septic pigs also receiving antibiotic treatment, although it can be argued that the ultrafiltration rate in that study was lower (60 mL/kg/h) than in the other HV-HF studies [40].

Table 1. Animal studies.

Author	Model	Study design		Intensity of treatment		Timing[1] (h)	HF mode[2]	Filter[3] (m^2)	Fluid resuscitation	Outcome	
		Treatment (number)	Control (number)	UF rate (mL/kg/h)	Duration (h)					Physiological	Clinical
Hemofiltration dose studies											
Murphey et al. [31]	Pig, LPS 10 μg/kg	S+HF (7); S+shamHF (4)	S (5); S+sham HF (4)	33	4	0.5	Post	PS	Crystalloid target Ht	–	NR
Toft et al. [32]	Pig, LPS 30 μg/kg	S+HF (10)	S (10); control (10)	35	22.5	0.7	Pre	PAN 1.0	Crystalloid target pressure	–	–
Heidemann et al. [30]	Rat, LPS 10 μg/kg	S+HF (6)	S+sham HF (6)	37	4	0.25	Post	PS	NR	–	+
Freeman et al. [40]	Dog, peritonitis	S+HF (7)	S (7); S+sham HF (7)	60	6	1	NR	PS	NR	–	–
Su et al. [38]	Dog, ALI	S+HF (5)	S (6)	50–65	4	2–3	Pre	PS 0.4	NR	+	NR
Lee et al. [4]	Pig, Saur sepsis	S+HF (20)	HF (4); S+ sham HF (20)	50–75	7	1	Post	PS	None	+	+
Bellomo et al. [23]	Dog, LPS 0.5 mg/kg	S + HF (8)	S (8)	80	3	Before sepsis	Pre	PAN 0.45	Crystalloid target pressure	+	NR
Yekebas et al. [36]	Pig, pancreatitis	S+LV-HF (12); S+LV-HF+FFR (12); S+HV-HF+FFR (12)	S (12)	LVHF: 20 HVHF: 100	60	14	Pre	PAN	NR	+	+
Wang et al. [35]	Pig, Pancreatitis	S+LV-HF (8); S+HV-HF (8)	S (8)	20 and 100	72	0	Pre	PAN	Crystalloid 5 mL/kg/h	+	NR
Yan et al. [39]	Pig, Pancreatitis	S+LV-HF (8); S+HV-HF (8)	S (8)	20 and 100	72	1	Pre	PAN 1.2	Crystalloid 5 mL/kg/h	+	+
Li et al. [37]	Pig, Pancreatitis	S+LV-HF (8); S+HV-HF (8)	S (8)	20 and 100	72	Before sepsis	Pre	PAN 1.2	Crystalloid 5 mL/kg/h	+	+
Ullrich et al. [34]	Pig, LPS 0.5 mg/kg	S+HF (6)	S (6); S+sham HF (4)	150–180	4	1	Pre	PS	Crystalloid target pressure	+	NR

Grootendorst et al. [3]	Pig, LPS 0.5 mg/kg	S+HF (6)	S (6); S+sham HF (6)	160	3.5	0.5	Pre	PS	Crystalloid 400 mL/h	+	NR
Grootendorst et al. [33]	Pig, SMA clamping	S+HF (6)	S (6); S+ sham HF (6)	172	2.5	Before clamping	Pre	CP	Crystalloid 600 mL/h	+	+
Rogiers et al. [5]	Pig, LPS 2 mg/kg	S+HF 3L/h (5); S+HF 6 L/h (5);	S (5); HF (5)	100 and 200	4.5	0.5	Post	PS 0.7	Crystalloid target pressure	+	NR
Hemofiltration dose and timing studies											
Yekebas et al. [65]	Pig, Pancreatitis S+early HF	(12); S+late HF (12)	S (11)	20	20	Early: 0 late: 1.75	NR	PS	Crystalloid 5 mL/kg/h	+	+
Mink et al. [64]	Dog, *P aer* sepsis	S+early HF (12); S+late HF (13)	S (13); shamS +early HF (4); S (13); shamS (4); shamS+ late HF (4)	33	3	Early: 2 late: 5	Post	PA 0.66	Colloid 5 mL/kg/h	+	NR
Yekebas et al. [66]	Pig, Pancreatitis	S+late LV-HF (12); S+early LV-HF (12); S+late LV-HF +FFR (12); S+early HV-HF (12); S+late HV-HF+FFR (12); S+early HV-HF+FFR (12)	S (12)	LVHF: 20 HVHF: 100	60	Early: 0 late:16	Pre	PAN	NR	+	+
Hemofiltration dose and filter studies											
Rogiers et al. [24]	Dog, LPS 2 mg/kg	S+PS (5); S+PAN (5)	S (5)	100	4.5	0.5	Post	PS 0.71 PAN 0.85	Crystalloid target pressure	+	NR
Veenman et al. [77]	Pony, LPS 2 μg/kg	S+HPHF (5)	S (5)	120	4.5	0.5	Pre	75 kDa PMMA	Crystalloid 5 mL/kg/h	–	NR
Lee et al. [68]	Pig, *S aur* sepsis	S+HF (7)	S+HPHF (7)	100–200	6	1.0	Post	PS 100 kDa PS	None	+	+

[1]Time between induction of sepsis and start of hemofiltration. [2]All studies used heparin for anticoagulation of the extracorporeal system. [3]All studies used conventional membranes allowing the removal of molecules up to 30 kDa. –: negative; +: positive; ALI: acute lung injury; CP: cuprophane; FFR: frequent filter replacement (every 12 h); HF: hemofiltration; HPHF: high permeability HF (*in vitro* cutoff 75–100 kDa); Ht: hematocrit; HV-HF: high-volume HF; LPS: *Escherichia coli* endotoxin; LV-HF: low-volume HF; NR: not reported; *P aer*: *Pseudomonas aeruginosa*; PA: polyamide; PAN: polyacrylonitrile; Pre: predilution HF; Post: postdilution HF; PMMA: polymethylmethacrylate; PS: polysulfone; S: sepsis or systemic inflammatory response syndrome; *S aur*: *Staphylococcus aureus*; shamHF: HF with clamping of the ultrafiltrate line; SMA: superior mesenteric artery; UF: ultrafiltrate.

Table 2. Human randomized controlled trials.

Reference	Study design		Patients	Intensity of treatment		Substitution type and mode	Blood flow (mL/min)	Filter (m^2)	*In vitro* cutoff (kDa)	Outcome	
	Treatment (number)	Control (number)		UF rate (mL/kg/h)	Duration (h)					Physiological	Clinical
Low-volume hemofiltration studies											
Sander et al. [42]	CVVH 1 L/h (13)	Control (13)	SIRS, no ARF	13	48	Ringer, NR	150	PAN	40	–	NR
Cole et al. [41]	CVVH 2 L/h (12)	Control (12)	Septic shock, no ARF	27	48	Lactate, predilution	200	PAN 1.2	40	–	–
Phu et al. [45]	CVVH 25 L/day (34)	PD (36)	Septic shock and ARF	14	Duration ARF or death	Lactate and bicarbonate, predilution	150	PA 0.66	30	NR	+
John et al. [46]	CVVH 2 L/h (20)	IHD (10)	Septic shock and ARF	26	96	Lactate, postdilution	250	PS 1.35	30	+	NR
High-volume hemofiltration studies											
Ronco et al. [44]	CVVH 35 mL/kg/h (17); CVVH 45 mL/kg/h (15)	CVVH 20 mL/kg/h (20)	Septic shock and ARF	20 35 45	Duration ARF or death	Lactate, postdilution	120–240	PS 1.3 and 1.7	35	NR	+
Cole et al. [52]	Short-term HV-HF 6 L/h (11)	CVVH 1 L/h (11)	Septic shock and ARF	13 80	8	Lactate one-third pre-, two-thirds postdilution	200 300	PAN 1.2 and 1.6	40	+	NR
Laurent et al. [54]	Short-term HV-HF 200 mL/kg/h (22); HV-HF+HT (20)	Control (19)	OHCA, no ARF	200	8	Bicarbonate, predilution	200	PA 1.2	40	+	+
Ghani et al. [55]	Short term HV-HF 6 L/h (15)	CVVH 2 L/h (18)	Septic shock and ARF	35 100	24 6	Bicarbonate half pre- half postdilution	200–250 250–350	PS 1.4	35	NR	–
High-volume hemofiltration and timing studies											
Jiang et al. [53]	HV-CVVH 4 L/h Early and late[1]	CVVH 1 L/h Early and late[1]	Pancreatitis No ARF	18 72	≥72	NR	250–300	PAN 1.2	40	+	+

[1]Early: <48 h after onset abdominal pain. Late: >96 h after onset abdominal pain.
–: negative; +: positive; ARF: acute renal failure; CVVH: continuous venovenous hemofiltration; HT: hypothermia; HV-HF: high-volume hemofiltration; IHD: intermittent hemodialysis; NR: not reported; OHCA: out-of-hospital cardiac arrest; PA: polyamide; PAN: polyacrylonitrile; PD: peritoneal dialysis; PS: polysulfone; SIRS: systemic inflammatory response syndrome; UF: ultrafiltrate.

Human studies

There is reasonable evidence that hemofiltration with lower volumes has no benefit in patients with sepsis without ARF [41,42] and that a dose of 35–45 mL/kg/h improves survival in critically ill patients with ARF [43,44]. In patients with septic shock and no ARF, two small RCTs compared the effects of CVVH using low exchange rates with no hemofiltration [41,42]. In these two studies, CVVH did not improve physiological [41,42] or clinical [41] endpoints and plasma levels of tumor necrosis factor and interleukin-6 (IL-6) and anaphylatoxins did not decrease. Of note, the study by Cole et al. was not powered to detect a tangible effect on organ dysfunction [41]. Two other small RCTs in patients with severe sepsis and oliguric ARF comparing low-volume CVVH with peritoneal dialysis [45] and intermittent hemodialysis [46] found that the delivered renal replacement dose should be adequate. Several uncontrolled clinical studies reported beneficial effects of low-volume CVVH on hemodynamics [47–50] but, because no control groups were included, it is not clear if these effects were hemofiltration-related. Ronco et al. performed the largest RCT on the effects of ultrafiltrate dose on outcome in critically ill patients with oliguric ARF with or without sepsis [44]. Patients were randomly assigned to treatment groups 1 (20 mL/kg/h), 2 (35 mL/kg/h), or 3 (45 mL/kg/h). The survival rate at 15 days after discontinuation of hemofiltration was significantly lower in group 1 (41%) compared with groups 2 (57%) and 3 (58%), indicating that a minimal renal dose of 35 mL/kg/h was required to improve survival rate in patients with ARF. In the subgroup of patients with sepsis (n=52), survival was 47% in group 3, compared with 18% in group 2 and 25% in group 1 (p=0.23), suggesting that sepsis patients might benefit from a higher ultrafiltrate dose. The upcoming multicenter study IVOIRE (High Volume in Intensive Care) addresses this and other issues [51]. Inclusion of 460 patients with septic shock of <24 h is planned, and subjects are to be randomized into early treatment with CVVH (35 mL/kg/h) or CVVH (70 mL/kg/h) for 96 h. The primary endpoint of the study is all-cause 28-day mortality and the study is expected to be completed in December 2008.

Only one larger and three small RCTs studied the effects of hemofiltration and ultrafiltration rates of >70 mL/kg/h [52–55]. The largest RCT (n=61) applied the highest ultrafiltration rate (200 mL/kg/h) for a duration of 8 h in patients following out-of-hospital cardiac arrest [54]. Patients exhibit a sepsis-like syndrome combined with increased endotoxin levels after cardiac arrest [56]. In the study of Laurent et al. [54], cardiac arrest patients were randomized to control or short-term HV-HF with or without hypothermia. The hemofiltration groups showed improved 6-month survival rates and a decreased risk of death from early, intractable shock. No significant effect of hemofiltration on IL-6 or anaphylatoxins was found. In a small crossover study in 11 patients with septic shock and ARF, Cole et al. compared short-term (8 h) HV-HF (80 mL/kg/h) with short-term low-volume (13 mL/kg/h) hemofiltration [52]. Significantly less norepinephrine was required to maintain target MAP (>70 mmHg) during HV-HF than during low-volume hemofiltration, and this was not caused by an effect on fluid balance. Other hemodynamic parameters did not change significantly over time during either therapy. Short-term HV-HF caused a greater reduction in the level of anaphylatoxins than low-volume hemofiltration. The concentration of mediators in the ultrafiltrate was negligible, suggesting adsorption as the major mechanism for mediator removal with this polyacrylonitrile filter. According to the authors, adsorption was higher during HV-HF because of higher transmembrane pressures and because a larger filter was used. In another very small RCT in 37 patients with severe pancreatitis, hemodynamics and short-term survival rate were significantly better during high-volume CVVH (70 mL/kg/h) than during low-volume CVVH (18 mL/kg/h) [53]. In a recent study, 33 septic shock patients were randomized to receive CVVH (35 mL/kg/h) or short-term HV-HF (100 mL/kg/h for 6 h) [55]. Although there was a significant reduction in IL-6 levels in the HV-HF group after 6 h of treatment compared with the CVVH group, there was no difference in the survival rate between the two treatment groups after 15 days.

Several observational studies showed beneficial effects of HV-HF on survival [57–61], hemodynamics [57,58,60–62] and oxygenation (Table 3) [62]. However, because these studies did not include control groups, it is not clear if the observed effects are hemofiltration-related. In a large observational study in septic patients (n=91) receiving ≥24 h of high-volume CVVH (63 mL/kg/h), the mortality rate was lower (33%) than predicted by the Acute Physiology and Chronic Health Evaluation II (APACHE II; 76%) and Simplified Acute Physiology II (SAPS II; 71%) illness severity scores [59]. In a smaller (n=24) observational study in septic patients, 96 h of high-volume CVVH (40–60 mL/kg/h) improved hemodynamics and decreased the need for catecholamine support [58]. The latter study also reported reduced observed 28-day mortality rates compared with the predicted rates; however, the scores used to determine these were not developed to predict 28-day mortality rates. Encouraging results of short-term (4 h) HV-HF (116 mL/kg/h) were reported in a small, prospective, uncontrolled study in patients with refractory hypodynamic septic shock [63]. Pre-determined hemodynamic goals were achieved in 11 of the

20 patients. Of these 11 responders, nine patients were still alive on day 28. All nonresponders died within the first 24 h. The observed mortality rate (55%) was significantly lower than the APACHE II- and SAPS II-predicted mortality rate (79%). Retrospective analysis showed that in the responders, ultrafiltrate volume was higher and hemofiltration was started earlier than in the nonresponders, suggesting that a high ultrafiltrate dose and an early start of hemofiltration could be important factors. Cornejo et al. recently reported similar beneficial results in patients with refractory septic hyperdynamic shock [61]. In that study, HV-HF (100 mL/kg/h) for 12 h was started as salvage therapy in the setting of a goal-directed hemodynamic management algorithm. Adjunctive HV-HF treatment resulted in decreased norepinephrine and lactate levels in 11 patients and, in these patients, hospital mortality rate (40%) was significantly lower than predicted. In another observational study in patients with sepsis, pulse HV-HF (85 mL/kg/h for 6–8 h followed by 16–18 h of 35 mL/kg/h) improved hemodynamics, allowing a reduction in norepinephrine dose [60]. Moreover, the observed 28-day mortality rate was 47%, whereas the predicted mortality rates were 72% (based on APACHE II) and 68% (based on SAPS II). As mentioned by the authors, the use of activated protein C in approximately 50% of the patients might have contributed to the improved outcome.

Further issues

The timepoint of initiating hemofiltration in the course of sepsis could be of major influence. In comparison with animal studies, hemofiltration in human studies is generally initiated late, as salvage therapy, in refractory septic shock or multiple organ failure [61,63]. From a pathophysiological standpoint, however, intervening at the earliest stage of the inflammatory cascade seems most plausible. In animal studies, early hemofiltration was found to have greater benefit, but it is important to realize that early hemofiltration – as defined in animal studies – is hardly feasible in clinical practice [64–66]. In humans, two studies show beneficial effects on survival rates with early timing, but these studies are either underpowered or retrospective in nature [53,57].

The type of filter could affect the removal of mediators. Although there is a physiological rationale to the use of highly adsorptive membranes, early membrane saturation limits its practical use [17,67]. A substantial removal of middle molecular weight substances can be achieved by increasing pore size of the membrane (*in vitro* cutoff 80–100 kDa) allowing the elimination of molecules with molecular weights up to 50 kDa [47,68,69]. However, a major drawback of this method is the loss of proteins other than cytokines, such as albumin. Thus far, the number of high molecular weight cutoff membrane clinical studies is small, but they show an effective removal of inflammatory mediators and suggest that the method is well-tolerated [26,70–73].

The prescribed dose is affected by the hemofiltration mode and by the continuity of the treatment. As mentioned above, the hemofiltration mode may have a dramatic influence on the clearance of mediators *in vivo*; however, thus far, no study has taken this aspect into account. In addition, the prescribed dose is often not the dose actually delivered, for example, as a result of premature clotting of the system.

Conceivable adverse effects of performing hemofiltration, particularly HV-HF, must be considered when defining indications. These include bleeding, catheter-related complications, frequent filter clotting, immunological adverse effects of the extracorporeal circulation [74,75], and increased loss of beneficial water-soluble substances (amino acids, vitamins, micronutrients). Of note, although HV-HF is associated with an increased loss of beneficial water-soluble substances, limitations of the venous access, and a higher tendency to filter clotting, human studies have not reported deleterious clinical effects. However, the highest ultrafiltration rates (>85 mL/kg/h) were never applied for longer than 12 h.

The majority of critically ill patients receive some form of antimicrobial treatment. Correct dosing during hemofiltration is of utmost importance and requires knowledge of the effects of extracorporeal clearance on total body clearance [76]. During hemofiltration, in particular HV-HF, it may be necessary to increase the dose of some antibiotics to compensate for the extracorporeal removal.

Conclusion

At this time, clinical evidence to recommend the application of HV-HF as an adjunctive therapy in sepsis without ARF is lacking. In patients with ARF and sepsis, there is reasonable evidence that a dose of 35–45 mL/kg/h improves survival rate, as compared with 20 mL/kg/h. The findings to date justify suitably powered RCTs on the effects of hemofiltration and high ultrafiltrate exchange rates. The upcoming results of the IVOIRE study may help to guide more firm recommendations in the future, although the many uncertainties regarding optimal volume, timing of initiation, duration of treatment, and type of membrane indicate that additional clinical studies are needed. In order to facilitate comparison among future studies, consensus definitions are mandatory, in particular for hemofiltration intensity and timing. Due to the many uncertainties, studies should first focus on endpoints such as recovery from organ failure and length of treatment before new survival studies

Table 3. Human observational studies.

Reference	Hemofiltration technique	Patients (numbers)	Intensity of treatment		Substitution type and mode	Blood flow (mL/min)	Filter (m2)	*In vitro* cutoff (kDa)	Outcome	
			UF rate (mL/kg/h)	Duration (h)					Physiological	Clinical
Low-volume hemofiltration studies										
Klouche et al. [48]	CVVH 1.5–2 L/h	Septic shock and ARF (11)	20–27	24	Bicarbonate, postdilution	250	PAN 0.8	30	+	-
Kruger et al. [49]	CVVH 40–45 L/day	Septic shock and ARF (19)	22	154±24	NR	NR	PA 0.88	40	+	-
Level et al. [50]	CVVH 2.5 L/h	Septic shock and ARF (13)	22	96	Bicarbonate postdilution	160	PAN 0.9 PA 1.4	30	+	NR
Hoffmann et al. [47]	CVVH 2 L/h	Septic shock and ARF (16)	27	24	Crystalloid, NR	150	PA 0.66	40	+	NR
De Vriese et al. [21]	CVVH using low or high blood flows	Septic shock and ARF (16)	20 33	24	Crystalloid, predilution	100 200	PAN 0.9	40	_	NR
High-volume hemofiltration studies										
Joannes-Boyau et al. [58]	HV-CVVH 40–60 mL/kg/h	Septic shock and ARF (24)	40–60	<96 (n=6) >96 (n=18)	Bicarbonate one-third pre, two-thirds post	200–300	PS 2.0	35	+	+
Oudemans-van Straaten et al. [59]	HV-CVVH 100 L/day	Sepsis/SIRS and ARF (91)	63	48–216	Bicarbonate or lactate postdilution	200	CTA 1.9	69	+	+
Wang et al. [62]	HV-CVVH 4 L/h	Pancreatitis, with (21) and without ARF (7)	72	120	NR	250–300	PAN 1.2	35	+	+
Ratanarat et al. [60]	Pulse HV-HF 85 mL/kg/h	Septic shock and ARF (15)	85	6	Bicarbonate half pre- and half post	250–300	PS 1.8	35	+	+
Cornejo et al. [61]	Short term HV-HF 100 mL/kg/h	hyperdynamic septic shock and ARF (20)	100	12	Bicarbonate predilution	200	PS 1.33	35	+	+
Honore et al. [57]	Short term HV-HF 35 L/4 h	hypodynamic septic shock and ARF (20)	116	6	Bicarbonate, NR	450	PS 1.6	35	+	+

–: negative; +: positive; ARF: acute renal failure; CTA: cellulose triacetate; CVVH: continuous venovenous hemofiltration; HV-CVVH: high-volume CVVH; HV-HF: high-volume hemofiltration; NR: not reported; PA: polyamide; PAN: polyacrylonitrile, PS: polysulfone; SIRS: systemic inflammatory response syndrome; UF: ultrafiltrate.

are started. Finally, a suitably powered RCT in humans should be preceded by a critical analysis of why this has not yet been undertaken. High costs, technical uncertainty, wide clinical variability, and absence of standard of concomitant treatment may have hampered the initiation of such studies.

Disclosures

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Surviving Sepsis Campaign Update: Local Data Collection Informs Global Quality Improvement Efforts

Adv Sepsis 2007;**6**(2):58–60.

With >7000 patient charts from 16 countries now in the global Surviving Sepsis Campaign (SSC) database (Fig. 1), Campaign leaders are able to state definitively that the Campaign will have an expanding influence on patient outcomes. At a meeting in Brussels, Belgium, in March 2007, the assembled executive committee members were able to point to specific elements of the sepsis bundles to determine next steps in the crux of the Campaign – the quality improvement process. According to SSC executive committee member Mitchell Levy, MD, "We set out to change how clinicians treat sepsis patients, and we're already seeing that the Campaign has made a difference in bedside care. We can identify those bundle elements that are completed consistently, and those that require additional attention, nearly across the board. Overall, the initiative appears to be working, and patients will be the better for it".

The improvement process

A special April 2007 edition of Campaign Update, the SSC's bi-monthly electronic newsletter, focused on the PDSA cycle – Plan-Do-Study-Act – as the basis of the improvement process [1,2]. The Campaign's data collection and reporting tools provide powerful resources to create change, by looking at individual bundle elements.

An initial review of the database at 20 months since its inception demonstrated that two elements of the 6-h resuscitation bundle related to the early goal-directed therapy measures – central venous pressure (CVP) and central venous oxygen saturation ($ScvO_2$) – are not being achieved (Fig. 2) [3]. The Campaign encourages participants to use the reporting tools provided to measure progress toward an internal goal of decreasing time from presentation to delivery of the early goal-directed therapy elements.

The SSC leadership is dedicated to providing regular reports from the global database to the participants as overall compliance data are documented during the Campaign's progression. Because facilities are at different points in the development and implementation process, the Campaign will provide a range of educational tools and resources for groups at varying levels. Opportunities to share experiences, tips, tools, and questions will continue to be provided by the Campaign via the newsletter, Listserv, local network and regional meetings, sessions at major international society meetings, and other publications.

Guidelines revision

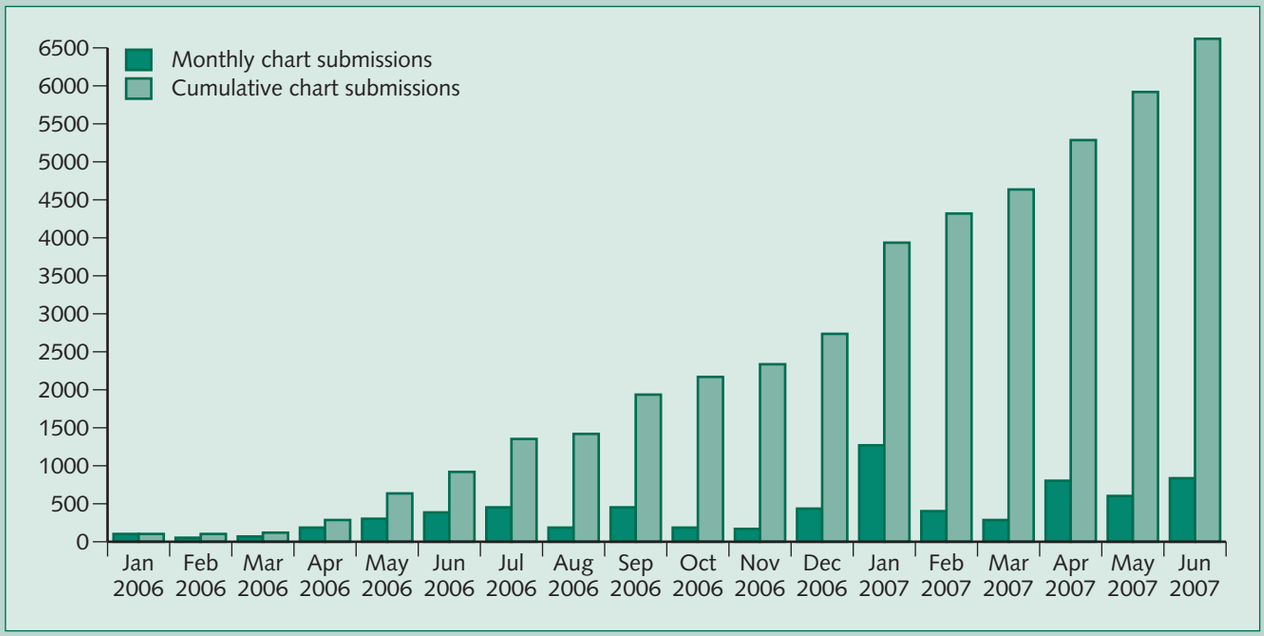
While Phase III of the Campaign, data collection, proceeds successfully with new facilities joining each week, a group of sepsis experts representing 16 different organizations met in person and communicated via email to bring to closure the first revision of the original guidelines published in March 2004 [4].

The revision is currently undergoing peer review for publication in *Critical Care Medicine* and *Intensive Care Medicine* as well as review by the participating organizations. In keeping with the historic nature of the first edition, the second edition will also reflect sign-on by global professional societies whose members are involved in the treatment of patients with severe sepsis and septic shock.

This edition will include recommendations based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system of evidence-based medicine. R Phillip Dellinger, MD, who headed the revision process, explains, "A limitation of the original system was that it used quality of evidence as the sole criterion for grading recommendations. In the GRADE system, variables used for determining the strength of recommendations include not only quality of evidence, but also risk of intervention, cost of intervention, consistency of literature support, and ability to conduct clinical trials in the presence of general acceptance of the intervention being graded".

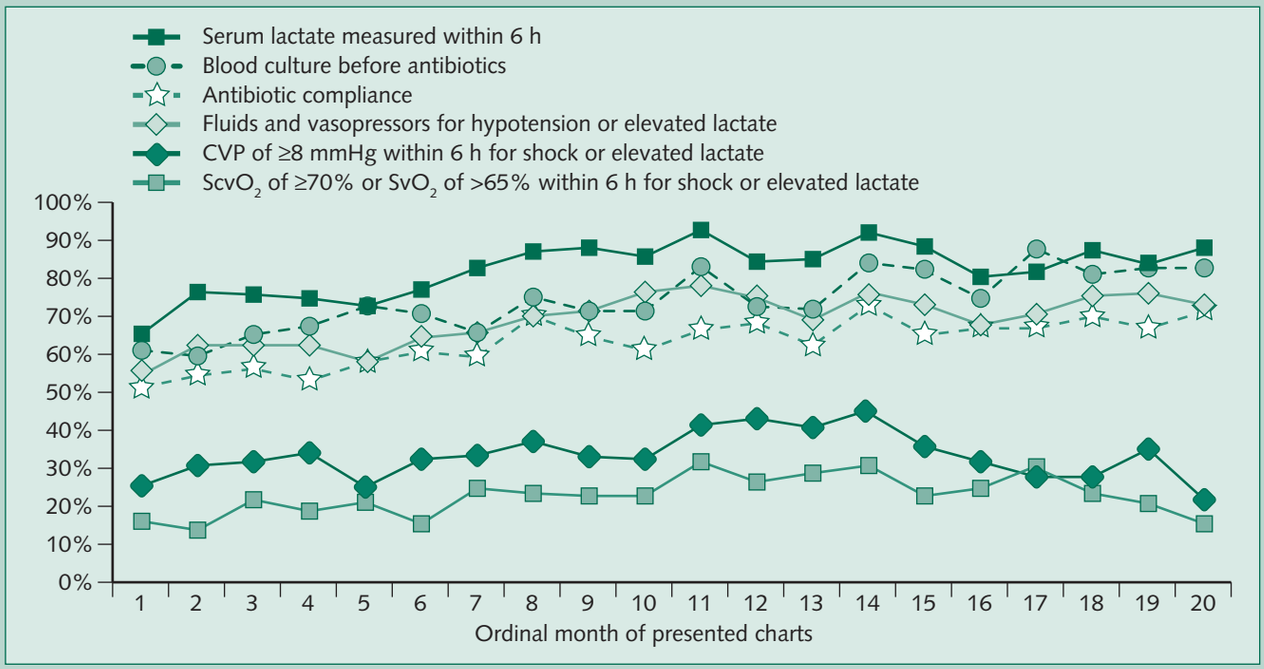
The revision will further the Campaign's goals to solidify a worldwide best practice for the management of patients with severe sepsis and septic shock. Through participation in the Campaign by collecting and contributing data and using it for

Figure 1. Total number of chart submissions to the Surviving Sepsis Campaign from January 2006 to June 2007.



Redrawn with permission from the Surviving Sepsis Campaign Campaign Update; July/August 2007.
http://www.survivingsepsis.org/system/files/images/Campaign_Update_7-07.pdf

Figure 2. Overall compliance with the individual elements of the 6-h resuscitation bundle during the 20 months the Surviving Sepsis Campaign has received data.



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http://www.survivingsepsis.org/system/files/images/April_2007_20Special_20Edition_1_.pdf
$ScvO_2$: central venous oxygen saturation; SvO_2: venous oxygen saturation.

performance improvement in their own facilities, thousands of clinicians around the world will be able to lay claim to having made major changes in patient outcomes.

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CLINICAL REVIEWS

Commentary and Analysis on Recent Key Papers

Clinical reviews were prepared by Daniel De Backer, MD, Nicholas Ward, MD, and Eric Wiel, MD

CLINICAL OBSERVATIONS AND RESEARCH

Brain lesions in septic shock: a magnetic resonance imaging study

Sharshar T, Carlier R, Bernard F et al.
Intensive Care Med 2007;**33**:798–806.

The authors of the present study used magnetic resonance imaging of the central nervous system to search for evidence of injury to the brain of patients with septic shock. The results showed that radiological evidence of injury is common, with white matter lesions the most frequent form seen. The severity of the lesions correlated with poor outcome.

Sepsis is characterized by injury to many organ systems. Central nervous system (CNS) dysfunction is a well-documented phenomenon in septic patients and usually manifests as decreased mental status or delirium. Previous *post mortem* studies have shown pathological evidence of brain injury in septic patients, but little is known about their timing and location. The authors of this study sought to gain further insight into sepsis-induced brain injury by performing magnetic resonance imaging (MRI) on patients with septic shock.

Patients were screened to exclude those with pre-existing CNS disease. Nine patients with vasopressor-dependent septic shock were included in this study. MRI scans found that a majority of patients (75%) displayed abnormalities thought to be the result of sepsis. MRI imaging was normal in two patients, identified multiple ischemic strokes in two patients, and showed white matter lesions at the level of the centrum semiovale, predominating around Virchow–Robin spaces and ranging from small, multiply affected areas to diffuse lesions, in the remaining five patients. The lesions of the white matter worsened with increasing duration of shock and were correlated with Glasgow Outcome Score.

This study provides evidence that the CNS dysfunction of sepsis is characterized by pathological injury to the brain. The most predominant injury appears to be leukoencephalopathy of the white matter, suggesting impaired permeability of the blood–brain barrier. Furthermore, the severity of the lesions correlated with outcomes.

Address for reprints: D Annane, Faculté de Médecine Paris Ile de France Ouest (UVSQ), Service de Réanimation Médicale, Hôpital Raymond Poincaré (APHP), 104 Boulevard Raymond Poincaré, 92380 Garches, France. Email: djillali.annane@rpc.aphp.fr

Circulating high-mobility group box 1 (HMGB1) concentrations are elevated in both uncomplicated pneumonia and pneumonia with severe sepsis

Angus DC, Yang L, Kong L et al.; GenIMS investigators.
Crit Care Med 2007;**35**:1061–7.

The authors of this study assayed blood samples from 122 patients with community-acquired pneumonia (CAP) for high-mobility group box 1 (HMGB1) protein throughout their illness. Their results showed that HMGB1 levels are greatly elevated in almost all CAP patients compared with control subjects. HMGB1 levels were not effective for discriminating between patients with sepsis and those without, and were poor at discriminating between survivors and nonsurvivors.

High-mobility group box 1 (HMGB1) is a protein that is released from a variety of immune systems cells in response to inflammatory stimuli such as lipopolysaccharide. Previous studies have shown plasma levels of HMGB1 to increase in humans during infections and sepsis, but the data are somewhat conflicting. The purpose of this study was to compare plasma levels of HMGB1 in patients with community-acquired pneumonia (CAP), CAP and sepsis, and severe versus non-severe sepsis.

The authors used plasma samples collected prospectively from patients and analyzed based on outcome. There were 122 patients with CAP, 49 of whom went on to develop sepsis and survived, while 30 developed severe sepsis and died. The results showed that HMGB1 levels were higher in

patients with CAP than in normal controls. However, there was no significant difference between levels in CAP patients with sepsis, and those without. HMGB1 levels were consistently higher in patients who died from sepsis than in those who survived, but both groups showed levels that were consistently high, making differentiation difficult. Interestingly, these data showed that high HMGB1 levels persisted in infected patients even after full recovery.

These results confirm earlier data showing HMGB1 can be used as a marker of CAP, given that levels are greatly elevated in almost all patients with CAP. Furthermore, plasma levels of HMGB1 correlate with survival rate but differentiating between those who lived and died would be difficult given the similarities of these levels.

Address for reprints: D Angus, Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Laboratory, University of Pittsburgh, Pittsburgh, PA, USA. Email: angusdc@upmc.edu

Impact of bolus application of low-dose hydrocortisone on glycemic control in septic shock patients

Weber-Carstens S, Deja M, Bercker S et al.
Intensive Care Med 2007;**33**:730–3.

The authors of the current study found that hydrocortisone bolus administration may be associated with transient alterations in glucose control, which can be minimized by continuous infusion at an equipotent dose.

Hydrocortisone administration in patients who require high doses of vasopressor agents has been recommended, based on the study by Annane et al. [1]. However, the mode by which hydrocortisone should be administered remains controversial. While the administration of a 50-mg dose every 6 h is the most commonly used approach [1], the administration of an equivalent daily dose as a continuous infusion may be considered. As a result of the bolus administration, some effects would be expected to oscillate due to the pulsatile changes in corticoid activity. In particular, glucose levels may fluctuate.

In this study, the authors evaluated the impact of bolus administration of hydrocortisone (50 mg) in 16 patients with septic shock receiving a continuous infusion of hydrocortisone (200 mg/day) and treated with intravenous infusion of insulin for glucose control (goal: glucose levels <150 mg/dL). The continuous infusion was suspended for 6 h to compensate for the bolus administration, and then resumed after 6 h. Blood glucose levels were measured every 4 h during continuous infusion, and the rate of glucose sampling was increased to once per hour during the 6 h following hydrocortisone bolus administration. The observation period covered 12 h before and 18 h after the bolus of hydrocortisone. Glucose administration was not modified during this observation period.

Glucose levels and insulin administration were stable during continuous hydrocortisone administration, both 12 h before and 6–18 h after the hydrocortisone bolus. In all patients, blood glucose levels increased within 6 h (peaking in most cases at 5 h) after the hydrocortisone bolus, and returned to baseline thereafter. However, there was great individual variability, with a minor increase in three, a decrease in four, and a marked increase in nine patients. Insulin administration required small adjustment of doses in some patients.

The principal limitation of this study is that the patients were receiving continuous hydrocortisone at baseline, so one may expect that the result would differ slightly in pulsatile administration, when baseline cortisol levels would be lower prior to hydrocortisone bolus administration.

Nevertheless, these preliminary results suggest that bolus hydrocortisone administration may be associated with more severe difficulties in controlling glucose levels compared with continuous administration. The clinical impact of this higher variability in glucose control remains to be determined, but it certainly increases the workload for nurses.

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Address for reprints: S Weber-Carstens, Universitätsmedizin Berlin, Clinic of Anesthesiology and Intensive Care Medicine, Charité, Campus Virchow-Klinikum & Campus Mitte, Augustenburger Platz 1, 13353 Berlin, Germany. Email: steffen.weber-carstens@charite.de

Association between high levels of blood macrophage migration inhibitory factor, inappropriate adrenal response, and early death in patients with severe sepsis

Emonts M, Sweep FC, Grebenchtchikov N et al.
Clin Infect Dis 2007;**44**:1321–8.

Circulating levels of macrophage migration inhibitory factor (MIF) were demonstrated to be increased in adult and pediatric patients with severe sepsis or septic shock, and elevated levels of MIF were correlated with several other mediators of sepsis, including lactate and cytokines. Moreover, levels of MIF were correlated with an increased risk of early death; thus, the authors propose the development of anti-MIF treatment strategies for these patients.

Macrophage migration inhibitory factor (MIF) is a key modulator of immune and inflammatory responses. There is evidence of crosstalk with corticosteroids and MIF-mediated

upregulation of Toll-like receptor 4. Furthermore, it has been shown to play an important role in experimental sepsis and acute respiratory distress syndrome. The present authors assessed the circulating levels of MIF in patients with sepsis, severe sepsis, or septic shock, the kinetics of MIF release and its interaction with other sepsis mediators, and the association of MIF with outcome.

Data from 68 adult patients who were previously enrolled in a study to assess the effects of an immunoglobulin G preparation in sepsis [1] were included in the present analysis. In addition, data from 77 pediatric patients who were enrolled in meningococcal sepsis studies at the Erasmus Medical Center (Rotterdam, The Netherlands) were analyzed [2–6].

In comparison with MIF levels in 196 healthy adult volunteers, serum levels in the adult patients with sepsis was significantly elevated at study entry (median level 103.7 ng/mL vs. 5.2 ng/mL; p<0.001), peaking at 2 h in the majority of patients, and remaining elevated for the duration of the analysis (final measurement at day 10). Peak MIF levels were correlated with levels of macrophage inflammatory protein-1β (p=0.001) and interleukin-1β (IL-1β) (p=0.05), and were inversely correlated with urine output (p=0.002).

In the pediatric patients, concentrations of MIF at study entry were correlated with the risk of mortality (p<0.001), and were higher in subjects with shock than in those who did not have shock (p<0.001). Furthermore, MIF levels were positively correlated with concentrations of lactate, procalcitonin, and cytokines including IL-1β, IL-1 receptor antagonist, IL-6, and IL-8.

Higher levels of MIF were associated with a rapid, early death in the adult patients studied, and were elevated in both adult and pediatric non-survivors compared with survivors (p<0.001). Interestingly, in the pediatric cohort, MIF concentrations were positively correlated with adrenocorticotrophic hormone (ACTH) levels, but negatively correlated with cortisol levels. This suggests a dysregulated adrenal response in meningococcal sepsis.

In summary, MIF was found to be elevated in adult and pediatric patients with Gram-negative sepsis and was correlated with other parameters of disease severity, and with rapid death. The investigators propose the development of anti-MIF treatment strategies in patients with severe sepsis and septic shock.

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Address for reprints: T Calandra, Infectious Diseases Service, Department of Medicine, Centre Hospitalier Universitaire Vaudois, CH 1011 Lausanne, Switzerland. Email: thierry.calandra@chuv.ch

Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality

Nguyen HB, Corbett SW, Steele R et al.
Crit Care Med 2007;**35**:1105–12.

The authors of this study demonstrated that sepsis bundle implementation in the emergency department is feasible. Bundle achievement was associated with an improved outcome.

It has been proposed that interventions that have been shown to improve outcome are grouped into bundles of care to be implemented in patients with severe sepsis. In this study, the authors investigated whether implementation of a severe sepsis bundle is feasible in the emergency department (ED) and whether compliance with the bundle would result in improvement in outcome. Several items were included in the bundle:

- Initiation of central venous pressure (CVP)/central venous oxygen saturation ($ScvO_2$) monitoring within 2 h.
- Administration of antibiotics within 4 h.
- Completion of early goal-directed therapy (CVP 8 mmHg, systolic blood pressure ≥90 mmHg or mean arterial pressure ≥65 mmHg, and $ScvO_2$ ≥70%) at 6 h.
- Administration of steroid if the patient was on vasopressor.
- Monitoring of lactate clearance.

This bundle was implemented in four successive phases over a 2-year period (October 2003 to September 2005): baseline (3 months), education (3 months), operational (3 months), and quality assessment (five successive periods of 3 months; quality indicator 1 [QI1] to QI5). A sepsis registry was prospectively established in order to evaluate the impact of the bundle. On a monthly basis, patient charts were reviewed and International Classification of Diseases-9 (ICD-9) codes suggestive of sepsis were used to identify patients with the condition. From these patient charts, individuals with septic shock (systemic inflammatory response syndrome [SIRS] criteria plus suspected infection and systolic blood pressure <90 mmHg after a 20 mL/kg fluid bolus or lactate levels ≥4 mmol/L) were identified. Patient data were entered into the registry and analyzed at the end of the study

period. Data entered included compliance with each part of the bundle, therapies administered, and outcome. The point at which a patient met the criteria for bundle initiation was considered as time 0.

A total of 330 patients were included in the study. Global adherence to the bundle increased over time, from approximately 10% during the first quality assessment quartile to 52% during the last quartile. Interestingly, rates of adherence to administration of antibiotics within 4 h and appropriate steroids were already high during the first quartile (89% and 85%, respectively) and remained stable over time. Conversely, rates of CVP/$ScvO_2$ monitoring by 2 h, early goal-directed therapy completed at 6 h, and lactate clearance improved over time.

Completion of the bundle was achieved in 77 patients and non-completion in 253. Despite similar severity at baseline in patients in the two groups, $ScvO_2$ was higher and lactate levels were lower in patients who completed the bundle compared with those who did not. Completion of the bundle was also associated with a lower mortality rate (21% vs. 40%). Analysis of the different components of the bundle showed that completion of all the components except CVP/$ScvO_2$ by 2 h was associated with an improved outcome.

The importance of this study is in its demonstration of the feasibility of bundle implementation, with satisfactory adherence. The impact of adhesion on outcome is more difficult to assess, especially since lactate clearance also reflects the response to therapy and not just the application of a specific therapy. In addition, some confounding and unmeasured factors associated with a poor outcome may have affected the enthusiasm of doctors to complete bundles.

Address for reprints: HB Nguyen, Department of Emergency Medicine, Loma Linda University, Loma Linda, CA 92354, USA.
Email: hbnguyen@llu.edu

Relationship between sublingual and intestinal microcirculatory perfusion in patients with abdominal sepsis

Boerma EC, van der Voort PH, Spronk PE et al.
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In this small study of patients with sepsis, sublingual and intestinal microvascular perfusion markedly diverged at the initiation of sepsis, but these differences tended to correct over time.

Recent studies have highlighted the role of microcirculatory alterations in the development of multiple organ failure in patients with septic shock [1,2]. However, evaluation of microcirculation at the bedside is restricted to the sublingual area, which is easily accessible for the small, hand-held microscopes currently used for this purpose (Orthogonal Polarization Spectral [OPS] microscope, with sidestream dark field imaging techniques). Thus, an important question remains: are the alterations observed in the sublingual area representative of other organs? Multiple experimental studies have shown that sepsis induces similar alterations in all organs investigated; however, it is possible that in some conditions, differences may occur between sites. In particular, during abdominal sepsis, it is possible that some local phenomena could interfere with the intestinal microcirculation, thus microvascular alterations may differ between this and the sublingual site.

Using an OPS device, the authors investigated the sublingual and intestinal microcirculation of 23 patients who developed sepsis and had a newly constructed stoma (ileum or colon). Twenty-nine non-septic control patients were also investigated, 19 with an old stoma and 10 with a newly constructed stoma. Microcirculatory blood flow was assessed using a semi-quantitative, non-continuous score – the mean flow index (MFI) score.

The MFI score was lower in septic patients than in control subjects, in both the sublingual area and the intestinal area. However, there was no correlation between microvascular scores in the intestinal area and those in the sublingual area at day 1. At day 3, the usual relationship was restored. The authors attributed this divergence to heterogeneity of sepsis-induced microvascular alterations, which tended to amend when sepsis resolved.

Alternatively, several factors may have specifically affected the intestinal microcirculation, being either relatively protective locally, especially when sepsis was minor (seven of the 23 patients had already been discharged on day 3), or having a more severe effect, particularly in the context of splanchnic ischemia (several patients were operated on for bowel infarction), or abdominal compartment syndrome. Finally, the method in which the score was calculated (with the MFI, the type of flow predominantly represented in one quadrant generates the score for this quadrant, and scores of different quadrants are later averaged) may have exaggerated some modest differences (especially in zones where 40–60% of the vessels are well-perfused); thus, different results may have been observed if other, more proportional scores had been used.

Regardless of the reasons for the differences in microvascular perfusion, they must be taken into account. In some patients, disparities between sites (here, sublingual and intestinal) may occur; therefore, an apparently normal sublingual microcirculation should always be considered cautiously, as other organs may still be compromised. The sublingual microcirculation is an easy window, considered to

be the common denominator, but other areas may continue to be more affected.

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Address for reprints: E Boerma, Department of Intensive Care, Medisch Centrum Leeuwarden, PO Box 888, 8901BR Leeuwarden, The Netherlands. Email: e.boerma@chello.nl

Serum lactate as a predictor of mortality in patients with infection

Trzeciak S, Dellinger RP, Chansky ME et al.
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These investigators determined that elevated lactate levels in patients with infection on admission to an emergency department are associated with a poor outcome, even after broad implementation of sepsis bundles.

Although the prognostic value of lactate levels at admission to an emergency department has been amply demonstrated, the introduction of resuscitation strategies triggered by measurements of lactate levels (such as early goal-directed therapy [EGDT]) may decrease the prognostic importance of this marker. The present authors evaluated the prognostic value of lactate level assessment – performed on admission into an emergency department – on outcome in patients with infection.

This was a *post hoc* analysis of a prospectively collected database. A lactate registry is used as a performance indicator in this institution, after implementation of EGDT and sepsis bundles. The registry was compiled in two stages. Firstly, a lactate report was generated automatically whenever lactate was measured, resulting in classification of the patient into a dedicated database. Secondly, the registry was linked to the central administration database allowing patient data to be retrieved according to specific keywords. The authors were able to identify 1177 patients, aged ≥18 years, with infection and serum lactate levels measured on admission between March 2004 and August 2005. Repeated hospitalizations were excluded. The outcome was evaluated as mortality at 3 days and at hospital discharge. Patients were stratified, according to lactate levels, into three groups: normal (<2 mEq/L), moderate (2–4 mEq/L), and high (>4 mEq/L). A Bayesian statistic approach was used to evaluate the additional value of lactate measurement (cutoff 4 mEq/L) on outcome prediction.

Lactate levels on admission were normal in 827 patients, moderate in 238, and high in 112. Hospital and 3-day mortality rate progressively increased with increasing admission lactate levels. More importantly, the Bayesian approach demonstrated that increased (>4 mEq/L) admission lactate levels improved outcome prediction compared with clinical judgment. Conversely, a negative test (lactate levels <4 mEq/L) did not improve outcome prediction.

Lactate levels can therefore be used as a warning signal; when positive, they suggest that the patient is at a higher risk of death although the absence of elevated lactate levels should not be considered reassuring.

Address for reprints: S Trzeciak, UMDNJ-Robert Wood Johnson Medical School at Camden, Cooper University Hospital, Division of Cardiovascular Disease and Critical Care Medicine and the Department of Emergency Medicine, One Cooper Plaza, Camden 08103, NJ, USA. Email: trzeciak-stephen@cooperhealth.edu

CLINICAL TRIALS

ADDRESS (ADministration of DRotrecogin alfa [activated] in Early stage Severe Sepsis) long-term follow-up: one-year safety and efficacy evaluation

Laterre PF, Abraham E, Janes JM et al.
Crit Care Med 2007;**35**:1457–63.

This study was a long-term follow-up analysis of the previously reported ADDRESS (Administration of Drotrecogin Alfa [Activated] in Early Stage Severe Sepsis) study of the safety and efficacy of drotrecogin alfa (activated) in patients with severe sepsis who were at a low risk of death. At this 1-year follow-up analysis, there was no difference in mortality rate between patients who received drotrecogin alfa (activated) and placebo (p=0.94). No additional serious adverse events were identified during this long-term assessment.

The efficacy of drotrecogin alfa (activated) (recombinant human activated protein C) in reducing all-cause mortality in patients with severe sepsis has been demonstrated; however, the benefit was shown to be greater in those at a higher risk of death. Thus, the ADDRESS (Administration of Drotrecogin Alfa [Activated] in Early Stage Severe Sepsis) study was initiated in order to assess the safety and efficacy of drotrecogin alfa (activated) in patients with "less severe" sepsis at a lower risk of death. In-hospital and 28-day safety and efficacy data from this randomized, placebo-controlled, double-blind study were previously reported [1].

A total of 2640 patients from 516 hospitals in 34 countries who were classed as having severe sepsis with a lower risk of death (generally defined as an Acute Physiology and Chronic Health Evaluation [APACHE] II score of <25 and/or single-organ dysfunction) were randomized to receive placebo or drotrecogin alfa (activated) in the initial

efficacy and safety analysis. However, enrolment was terminated due to the low likelihood of meeting the defined objective of a reduction in 28-day mortality in these patients with a low risk of death [1]. The present report describes the 1-year safety and efficacy outcome (long-term follow-up) of the ADDRESS study.

The long-term survival status of 90% of the patients initially enrolled was available for this analysis. Long-term mortality rates were similar in patients who had received drotrecogin alfa (activated) (n=1200) or placebo (n=1176) (34.2% vs. 34.0%; p=0.94). Subgroup analyses of patients with APACHE II scores of <25 or ≥25, single or multiple-organ dysfunction, identified no differences in survival between patients who received placebo and drotrecogin alfa (activated). No additional serious adverse events were reported during this long-term follow-up period and none of the deaths were considered to be due to the drug.

Although drotrecogin alfa (activated) appears to be safe at this 1-year follow-up in patients with severe sepsis who are considered to be at a low risk of death, no beneficial effects of the drug over placebo were identified in these individuals.

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Address for reprints: P-F Laterre, Departement of Intensive Care, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, 1200, Belgium.

Adrenal function in sepsis: the retrospective Corticus cohort study

Lipiner-Friedman D, Sprung CL, Laterre PF et al.
Crit Care Med 2007;**35**:1012–8.

In this retrospective study, the association of different definitions of adrenal dysfunction with patient outcome was tested. A change of ≤9 μg/dL cortisol level above baseline (Δ cortisol) was associated with a poor outcome, while basal and peak cortisol levels were not.

The role of adrenal dysfunction in the blunted vasopressor response in sepsis has been widely demonstrated [1–3], and hydrocortisone supplementation may even improve outcome; however, whether adrenal function should be tested remains unclear. Although the whole hypothalamic–pituitary–adrenal axis can be affected [4,5], adrenal function is the only factor assessed in clinical practice.

The most common method of testing adrenal function is to perform the corticotrophin (adrenocorticotrophic hormone [ACTH]-stimulation) test. However, several issues remain challenging, including determining correct dose [6,7], timing of measurements [6], and definitions of adrenal dysfunction [4,7,8]. Most studies have been relatively small in size. The present authors conducted this study to compare the predictive value of various definitions of adrenal dysfunction for outcome.

In this retrospective, multicenter study, the authors collected data on patients with sepsis in whom ACTH testing had been performed (dose 250 μg). In addition, patients who were participants in a previous study [3] were included, giving a total of 562 patients evaluated. Analysis was restricted to 477 patients after exclusion of patients treated with steroids (n=16) or immunosuppressive agents (n=20), those who were HIV positive (n=37) or who had recent cardiac arrest (n=8), those aged <18 years (n=2), and those with incomplete data for the ACTH test (n=2).

Data on cortisol values at baseline and at 30- and 60-min post-ACTH test were collected. In addition, demographic data, outcome data, and duration of vasopressor requirements were collected.

Of the 477 patients, 442 (93%) were mechanically ventilated and 253 (53%) were in shock. A total of 44% the patients received hydrocortisone, either just after the test or in the following days. Half of the patients had received etomidate ≥24 h before ACTH testing.

The incidence of adrenal dysfunction depended on its definition, ranging from 51% (post-stimulation cortisol value of ≤25 μg/dL) through 64% (a change of ≤9 μg/dL above baseline in cortisol level [Δ cortisol]) to 71% (baseline cortisol value ≤15 μg/dL or Δ cortisol ≤9 μg/dL). The hospital mortality rate was 60%. While definitions of adrenal dysfunction, including a Δ cortisol level of ≤9 μg/dL were associated with a higher risk of death, this was not the case when the definition only took into account the absolute value of cortisol after the ACTH test. Receiver operating curve (ROC) analysis confirmed this finding, as the ROC area was higher with Δmax measurement (peak cortisol minus baseline cortisol) compared with the peak cortisol value (0.63 vs. 0.52; p<0.05).

The impact of timing of cortisol measurement was also evaluated. Although cortisol levels were generally higher at 60 min than at 30 min, in 141 patients peak cortisol levels were higher at 30 min than at 60 min. In most cases, measuring cortisol at 60 min only would not have altered the classification, although 20 patients would have been misclassified. The authors stated that this is negligible; however, it accounts for a significant number of false-negative responders (4%), which may be relevant if therapy is based on the ACTH test. Interestingly, prediction of outcome was not affected by the timing of measurements, as difference from baseline at 30 min or 60 min, and Δmax yielded similar ROC area values (0.63, 0.62, and 0.62, respectively).

There were several limitations to this study. Firstly, it was conducted in patients with sepsis and was not restricted to septic shock. The relevance of adrenal dysfunction in non-shock patients remains to be demonstrated. Secondly, it was a retrospective study and the method in which patients were selected was not clear. Although it is stated that data on 77% of the patients were extracted from previously published studies [3], the number of patients in shock (n=253) was lower than that in one of the largest studies included in that database (n=299). This implies that either many of the patients were excluded for reasons not mentioned in exclusion criteria or that most of the remainder of the 477 patients included in this study were not in shock (but then it is unclear why many of these were treated with steroids after the ACTH test: in total, 210 patients received steroids). In addition, another large database held by one of the authors of the manuscript was not included [8]. Thirdly, the incidence of relative adrenal dysfunction was higher than in other studies using a similar definition [6,8]. Fourth, the mortality rate was quite high in this cohort. Finally, the high frequency of steroid use (n=210, representing 44% of the cohort) limits the interpretation of these results based on outcome. Although it is stated that the results based on the entire cohort did not differ from those based on the cohort of patients not receiving steroids, this is somewhat contradicted by the demonstration of a beneficial impact of steroid administration on outcome, as identified by multivariate analysis.

Overall, these findings confirm previous data [8], suggesting that a Δ cortisol level of ≤ 9 μg/dL can be used as the best cutoff to identify adrenal dysfunction.

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Address for reprints: D Annane, Service de Réanimation, Hôpital Raymond Poincaré (APHP), Faculté de Médecine Paris Ile de France Ouest (UVSQ), 92380 Garches, 104 boulevard Raymond Poincaré, Paris, France. Email: djillali.annane@rpc.ap-hop-paris.fr

DIAGNOSIS AND ASSESSMENT

Prognostic value of low blood glucose at the presentation of *E. coli* bacteremia

Alamgir S, Volkova NB, Peterson MW.
Am J Med 2006;**119**:952–7.

In this retrospective study, a correlation between low-dose glucose and death in septic *Escherichia coli*-infected patients was demonstrated. The source of infection in patients in whom this correlation was observed was, most commonly, the genitourinary tract. The exact mechanism of this association remains unclear and further investigation is required to confirm the importance of introducing aggressive therapy with the aim of reducing the mortality rate when sepsis presents with low blood glucose levels.

Even if low blood glucose is a well known complication of sepsis, its prognostic role has been less well studied. In this US study in which *Escherichia coli* was the most common bacteria responsible for sepsis, the incidence and prognostic value of low blood glucose at the presentation of sepsis were retrospectively studied in a community hospital setting.

Low blood glucose, defined as a blood glucose level of <70 mg/dL, was present in 4.6% of the 955 patients that presented with *E coli* bacteremia. The existence of diabetes (prevalence of 37%) did not influence the frequency of low blood glucose levels. The source of infection was correlated with low blood glucose for genitourinary infection and an unknown source. The latter is one of the limitations of the study design as the source was defined as unknown if the records did not report the source of infection. Thus, it remains difficult to conclude this association exhaustively. However, it appeared that genitourinary sources of *E coli* infection were significantly correlated with low blood glucose (odds ratio 6.23). The basis of this association remains unclear. Regarding outcome, patients with low blood glucose had a 4.7-times higher risk of death compared with patients who did not have low blood glucose. Being male and the presence of renal and liver dysfunction increased the risk of dying. Complex mechanisms are likely to underlie the involvement of the liver. The authors emphasized that *E coli* may affect glucose homeostasis through a direct or indirect effect on hepatocyte function.

This study has some limitations: its retrospective design with associated loss of data or non-recorded data, only *E coli* infection was assessed, and the study was performed in just one community hospital (it may differ in another hospital). Finally, the mechanism by which low blood

glucose is correlated with death has not been identified and requires further investigation. However, the study suggests that if a low blood glucose level is observed at presentation of sepsis, aggressive therapy should be introduced in order to reduce mortality rates. This remains to be demonstrated in a prospective, randomized study.

Address for reprints: NB Volkova, Department of Medicine, UCSF Fresno Medical Education Program, 445 South Cedar Avenue, Fresno, CA 93702, USA. Email: natalia.volkova@fresno.ucsf.edu

The prognostic value of muscle StO_2 in septic patients

Creteur J, Carollo T, Soldati G et al.
Intensive Care Med 2007;**33**:1549–56.

Microcirculatory alterations play an important role in the pathophysiology of sepsis. Microvascular dysfunction can be assessed in humans by examination of reactive hyperemia, and near-infrared spectroscopy (NIRS) can be used to quantify tissue oxygenation. This study demonstrated that muscle tissue oxygenation is altered after an ischemic challenge in septic conditions, and is associated with the severity of the disease. Its persistence is associated with a worse outcome. NIRS appears to be a useful tool and a novel method for evaluating the effects of sepsis therapies.

Sepsis is characterized, in part, by microcirculatory alterations with decreased vascular density and non-perfused/intermittently perfused vessels due to increased leukocyte and red blood cells adhesion, tissue edema, microthromboses in vessels, and endothelial cell injury leading to vascular tone dysfunction. Sepsis-induced microvascular dysfunction can be quantified by near-infrared spectroscopy (NIRS) using the differential absorption properties of oxygenated and deoxygenated hemoglobin evaluating skeletal muscle oxygenation. NIRS monitors vessels with a diameter of <1 mm [1]. It has been shown that reactive hyperemia can determine microcirculatory reactivity [2]. This allows evaluation of the ability of the tissue to adjust oxygen extraction capabilities to oxygen delivery after a hypoxic stimulus induced by a transient blood flow interruption. In septic conditions, reactive hypermia is altered. The goal of the study presented here was to quantify sepsis-induced alterations in muscle tissue oxygenation (StO_2) variation and the relationship with sepsis outcome.

Seventy-two patients were enrolled within 24 h after the onset of severe sepsis (n=24) or septic shock (n=48). After stabilization of mean arterial pressure (MAP) at >65 mmHg, StO_2 was measured with a NIRS probe placed on the skin of the thenar eminence. Following a 3-min period to stabilize the signal (StO_2 baseline), blood arterial flow was stopped for 3 min by inflating the arm sphygmomanometer cuff to 50 mmHg above the systolic arterial pressure. StO_2 was measured continuously during this 3-min period of ischemia and continuously for 3 min afterwards. Changes in StO_2 were defined by the slope of increase in StO_2 after the ischemic phase, and the difference between StO_2max (hyperemic phase) and baseline StO_2 (Δ). Severe sepsis and septic shock patients were compared with acutely ill patients without infection (defined as the control group), and healthy volunteers. It was shown that baseline StO_2 and the rate of StO_2 increase in the hyperemic phase were lower in septic patients (baseline StO_2: 72% in septic group vs. 80% in control group and 78% in healthy volunteers; rate of StO_2 increase: 2.6% in septic group, 4.7% in control group, 4.8% in healthy volunteers). The Δ value and the StO_2 slope were lower in septic patients. In the septic group, the slopes were lower in patients with shock compared with those without shock. No correlation was observed between the slope and the MAP, the arterial lactate level, and the norepinephrine dose. These results suggested – even if NIRS does not directly measure microcirculatory blood flow – that the slope and the Δ reflected the degree of the hyperemic reaction. The lower StO_2 value in septic patients may be explained by decreased oxygen delivery to the tissue. The second goal of the study was to demonstrate a relationship between StO_2 and outcome. The intensive care unit mortality rate in septic patients was 49%. In 52 septic patients in whom the slope was obtained at 24 h and 48 h, the slopes were higher in survivors than in non-survivors. These results demonstrated that the persistence of an altered recovery of muscle StO_2 after the ischemic challenge in septic patients is associated with a poor outcome. The authors highlighted some limitations to their study concerning NIRS technology. StO_2 is an average value of hemoglobin oxygen saturation in arterioles, venules, and capillaries and there is no distinction between these vessels. NIRS does not measure microcirculatory blood flow, and measurements can be altered by adipose tissue thickness or the presence of edema.

In conclusion, muscle tissue oxygenation is altered after an ischemic challenge in septic conditions, and is associated with the severity of the disease. Its persistence is associated with a worse outcome. NIRS seems to be a useful tool, which may be useful for the evaluation of the effects of sepsis therapies.

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Address for reprints: J-L Vincent, Erasme University Hospital, Free University of Brussels, Department of Intensive Care, Route de Lennik 808, 1070 Brussels, Belgium. Email: jlvincen@ulb.ac.be

Renal failure in septic shock: predictive value of Doppler-based renal arterial resistive index

Lerolle N, Guérot E, Faisy C et al.
Intensive Care Med 2006;**32**:1553–9.

The authors of this study sought to determine if there was a relationship between renal artery vasoconstriction on day 1 of sepsis and future renal failure. They used a resistive index (RI) calculated from Doppler ultrasound studies to show that a high RI on day 1 correlated with renal failure on day 5.

Acute renal failure (ARF) is common in sepsis and is thought to occur both through hemodynamic failure and via the effects of toxic mediators produced in inflammation. While many patients show abnormalities of kidney function early in sepsis, a smaller fraction will continue to have renal dysfunction at a later stage. Further understanding and treatment of this condition would be greatly aided by being able to determine which patients with septic shock will go on to have ARF. Previous data have determined that renal arterial blood flow can be diminished, even after hemodynamics have been corrected in septic shock. The authors of this study sought to determine whether renal artery constriction in sepsis was predictive of ARF.

A total of 37 patients with septic shock in a medical intensive care unit, excluding patients who had chronic renal failure, were studied. The investigators used renal artery Doppler ultrasound on day 1 of sepsis to determine a resistive index (RI). Additional data such as severity scores, vasopressor dose, and lactate levels were also assessed. Of the 37 patients, 35 were able to have an RI calculated. On day 5, 18 patients had ARF and 17 did not. The data showed that RI on day 1 was higher in the patients with ARF on day 5 (0.77±0.08 vs. 0.68±0.08; $p<0.001$). An RI of >0.74 on day 1 had a positive likelihood ratio of 3.3 (95% confidence interval 1.1–35) for developing ARF on day 5. Those with ARF on day 5 also had a higher Simplified Acute Physiology Score and a higher arterial lactate concentration.

This study demonstrates that a higher RI on day 1 of sepsis is predictive of later renal failure and suggests a possible correlation between renal artery vasoconstriction and ARF in patients with septic shock. It was limited by its small size and the lack of control over vasopressor dose administered to each patient. Further studies may provide more data on the role of renal artery vasoconstriction in the renal failure observed in patients with sepsis.

Address for reprints: N Lerolle, Université Paris-Descartes, Faculté de Médecine, Assistance Publique–Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Service de Réanimation Médicale, 20, rue Leblanc, 75908 Paris Cedex 15, France. Email: nicolas.lerolle@egp.aphp.fr

Longitudinal studies of inter-alpha inhibitor proteins in severely septic patients: a potential clinical marker and mediator of severe sepsis

Opal SM, Lim YP, Siryaporn E et al.
Crit Care Med 2007;**35**:387–92.

The authors of this report demonstrated that levels of the broad-spectrum protease inhibitor, inter-α-inhibitor (IαI), were significantly reduced in plasma of patients with severe sepsis, during the first 5 days. Lower levels were associated with increased age, female sex, and with multiple organ failure. Failure to recover levels during the 5 days of measurement resulted in significantly increased 28-day mortality rate, suggesting an important role of this endogenous protease inhibitor during the early phase of severe sepsis.

There is evidence to indicate that there is excessive endogenous protease activity in sepsis, in addition to a deficiency of protease inhibitors. The present authors examined the levels of the broad-spectrum, serine protease inhibitor, inter-α-inhibitor (IαI) protein, in plasma samples of patients with severe sepsis. Serial measurements of IαI were taken during the first 5 days, with the aim of identifying any correlations with other clinical and laboratory parameters of sepsis.

A total of 266 patients randomly selected for inclusion in this study from a larger Phase III, randomized, clinical trial of platelet-activating factor (PAF) acetylhydrolase [1]. Data were compared with those from 60 healthy volunteers. The mean age of the control population was significantly lower than that of the patients (43.0±10.2 years vs. 60.5±2 years).

At the onset of severe sepsis, the mean plasma concentration of IαI protein was significantly less than that in normal plasma (290±15 μg/mL vs. 617±197 μg/mL), although levels in severe sepsis did not differ significantly based on Acute Physiology and Chronic Health Evaluation (APACHE) II score, Multiple Organ Dysfunction Score, PAF acetylhydrolase treatment, or white cell count.

IαI protein concentrations were significantly lower in individuals who had an intra-abdominal source of sepsis, and these patients had the highest 28-day mortality rates. Furthermore, IαI levels were significantly lower in women, in older patients, and in those with multiple organ failure. Levels of IαI gradually increased over the 5-day assessment period; however, 3-day and 5-day levels were significantly lower in non-survivors compared with survivors at 28 days ($p<0.05$).

This study provides interesting data on a potential therapeutic strategy in severe sepsis, although further

preclinical and clinical trials are required to fully identify the utility of proteases such as IαI in the condition.

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Address for reprints: SM Opal, Infectious Disease Division, Brown Medical School, Providence, and Memorial Hospital of Rhode Island, Pawtucket RI 02860, USA.

PATHOGENESIS

Protein C -1641 AA is associated with decreased survival and more organ dysfunction in severe sepsis

Walley KR, Russell JA.
Crit Care Med 2007;**35**:12–7.

The present authors undertook a genotyping analysis of cohorts of patients with severe sepsis, and demonstrated that the AA genotype at position –1641 of protein C was associated with an increased mortality rate, more clinical evidence of systemic inflammation, and more organ dysfunction in these individuals, compared with the AG or GG genotypes.

Recombinant human activated protein C (rhuAPC, drotrecogin alfa [activated]) reduces the mortality rate in patients with severe sepsis who are at a high risk of death. A polymorphism in the protein C promoter region (–1641 A/G) has been shown to be associated with decreased levels of protein C and an increased risk of thrombotic events in patients with deep-vein thrombosis and pulmonary embolism. Thus, the present authors tested the hypothesis that the presence of this promoter polymorphism results in an altered outcome in patients with severe sepsis. Three cohorts of patients were included in the analysis:

- A derivation cohort of white patients with severe sepsis admitted to the intensive care unit of St Paul's Hospital, Vancouver, BC, Canada (n=62).
- A replication cohort of similar patients (n=402).
- A "biological plausibility" cohort of patients who underwent cardiopulmonary bypass surgery (a non-septic trigger of coagulation/inflammation) (n=61).

The primary endpoint for the first two cohorts was 28-day survival, and for the third cohort was postoperative interleukin-6 (IL-6) level. Patient characteristics at baseline did not differ according to genotype at position –1641.

Analysis of the derivation cohort of patients with severe sepsis demonstrated that AA at position –1641 of protein C was associated with a 61% survival rate, while the presence of AG or GG was associated with a survival rate of 84% at 28 days ($p<0.05$). This was confirmed in the analysis of the larger cohort of severe sepsis patients, with a decreased survival rate (58%) and a significant increase in Cox hazard ratio of death of 1.43 for the –1641 AA protein C genotype ($p=0.033$). Significantly more renal, neurological, hematological, and hepatic organ dysfunction was present in patients with the –1641 AA protein C genotype, as was clinical evidence of systemic inflammation. An increase in IL-6 levels in cardiopulmonary bypass surgery patients with the –1641 AA protein C genotype was also identified ($p=0.024$), which confirms the association of the genotype with systemic inflammation.

The authors highlight several limitations to their study, including the heterogeneity of the causes of severe sepsis – which were not controlled for in this analysis, the lack of measurement of cytokines, the potential for an indirect genetic effect, and other possible functional protein C polymorphisms.

However, the study demonstrates that the presence of the –1641 AA protein C genotype was associated with an increased mortality rate, more organ dysfunction, and more clinical evidence of systemic inflammation in critically ill patients with severe sepsis.

Address for reprints: KR Walley, Critical Care Research Laboratories, St Paul's Hospital and University of British Columbia, 1081 Burrard Street, Vancouver, BC, Canada V6Z 1Y6.

Myocardial lactate deprivation is associated with decreased cardiovascular performance, decreased myocardial energetics, and early death in endotoxic shock

Levy B, Mansart A, Montemont C et al.
Intensive Care Med 2007;**33**:495–502.

The authors of this study modulated lactate production in an endotoxic rat model of sepsis in order to determine the role of lactate as a substrate for myocyte metabolism. Their data show that inhibition of lactate production in sepsis has a deleterious effect on myocyte function, hemodynamics, and survival. These data suggest that lactate is an important substrate for myocyte metabolism in sepsis.

Septic shock is characterized by an array of metabolic and physiological disorders. One prominent feature of the condition is high lactate production by skeletal muscle, a phenomenon that appears to be stimulated by adrenergic activation with epinephrine. Reversible cardiac dysfunction caused by myocyte impairment is another prominent feature of septic shock and many cytokines and other mediators have been implicated as the cause of this. As the heart is known to use lactate as an energy substrate, the authors of

this article sought to determine whether the availability of lactate was associated with the cardiac dysfunction observed in sepsis.

The investigators used a lethal rat model of endotoxin-induced sepsis to measure and control lactate production in several ways. ICI 11851, a selective β2 adrenoceptor blocker, was used to inhibit the formation of lactate by adrenergic stimulation, and dichloroacetate was added for further inhibition. The authors found that hemodynamics, cardiac function, and survival rate were substantially worse when lactate was inhibited via either or both of these chemicals. Infusion of lactate attenuated these effects suggesting that lactate availability is an important component of cardiac function in endotoxin-induced sepsis.

These results show that the inhibition of lactate formation leads to deleterious effects on cardiac hemodynamics and survival rates in septic shock. They support the theory that the high lactate levels seen in sepsis are somewhat adaptive and that lactate is not just a metabolic waste product, but an important source of metabolism for the heart. The authors suggest that clinicians be cautious in using pharmacological agents that may modulate lactate metabolism.

Address for reprints: B Levy, Université Henri Poincaré Nancy 1, Coordination Circulation UHP-INSERM, Groupe CHOC, Faculté de Médecine, Nancy, France. Email: b.levy@chu-nancy.fr

Plasma-induced endothelial oxidative stress is related to the severity of septic shock

Huet O, Obata R, Aubron C et al.
Crit Care Med 2007;**35**:821–6.

In this study, reactive oxygen species were generated by exposing naïve human endothelial cell cultures to the plasma of patients with septic shock. The magnitude of this reaction was higher in non-survivors compared with survivors.

Oxidative stress is generated by reactive oxygen species (ROS). These are a component of the response to host invasion but can also lead to endothelial damage and contribute to multiple organ failure. Therefore, identification of oxidative stress is crucial for understanding the pathophysiological process of septic shock. Measurement of oxidative stress is difficult as many ROS are short-lived and unstable. In addition, various anti-oxidant substances aim to counterbalance the effects of pro-oxidant molecules, and thus measuring just a few substances may be misleading. In this article, the authors used an alternative approach to evaluate oxidative stress – testing the capacity of plasma to induce ROS production in naïve endothelial cell cultures.

Plasma from 21 consecutive patients with septic shock was obtained on days 1, 3, and 5. Exclusion criteria were moribund state, neutropenia, hemodialysis, or immunosuppressive therapy. Human umbilical vein endothelial cell (HUVEC) cultures were used to assess plasma oxidative stress. These cells were exposed to the plasma of healthy volunteers or plasma from septic patients, and ROS generation was identified using a fluorescent probe. In addition, the extent of lipid peroxidation in plasma and red blood cells was evaluated measuring plasma and red blood cell thiobarbituric acid-malondialdehyde levels. The activity of superoxide dismutase, glutathione peroxidase, and catalase was also measured. The redox status in red blood cells was evaluated by the ratio between glutathione disulfide (GSSG) and reduced glutathione (GH); vitamin E and A were also measured.

At day 1, plasma from patients with septic shock induced significantly higher ROS generation by HUVEC cells than plasma from healthy volunteers. In addition, ROS generation was higher in non-survivors than in survivors throughout the observation period. Interestingly, changes in ROS generation correlated with changes in sequential organ failure assessment score. The activity of glutathione peroxidase and catalase, but not that of superoxide dismutase, was lower in the blood of patients with septic shock compared with that from healthy volunteers. Plasma and red blood cell thiobarbituric acid-malondialdehyde levels and GSSG:GH ratio were higher in patients with septic shock compared with healthy volunteers, while vitamin A levels were lower. There was no difference in vitamin E levels.

These data indicate that plasma oxidative capacity is increased in patients with septic shock. Moreover, its association with a greater severity of shock suggests that this phenomenon may be implicated in the pathophysiology of septic shock. However, it should be remembered that these data demonstrate an association, not a causal link. Some oxidative stress may be beneficial, and its overexpression may just represent a greater activation of host defenses. Finally, one cannot completely exclude a potential role for nitric oxide (NO) activation in this ROS generation. Although the timing is too short to implicate inducible NO synthase, endothelial NO synthase may be activated by components of septic plasma. Whether this would be a beneficial or detrimental effect remains to be elucidated. Only interventional studies, blocking or minimizing ROS generation, will address these issues.

Address for reprints: O Huet, Département D'Anesthésie Réanimation, UPRES EA 3540, Université Paris XI, Hôpital Bicêtre, Le Kremlin Bicêtre, Paris, France.

THERAPEUTICS RESEARCH

Effects of levosimendan and dobutamine in experimental acute endotoxemia: a preliminary controlled study

Dubin A, Murias G, Sottile JB et al.
Intensive Care Med 2007;**33**:485–94.

Levosimendan has both vasodilator properties via stimulation of ATP-sensitive potassium channels in vascular smooth muscle cells, and calcium-sensitizing inotropic effects. These properties may circumvent tissue hypoperfusion by recruiting microcirculation. In this non-lethal, moderately resuscitated endotoxic shock model, levosimendan was shown to prevent the reduction in intestinal blood flow and diminish the development of intramucosal acidosis when compared with dobutamine. This effect was associated with a correction of pulmonary hypertension.

Sepsis is characterized by both heart and peripheral circulation alterations. Even if fluid challenge and vasoactive drugs do stabilize hemodynamic variables, gut perfusion may still be impaired, in association with persistent intramucosal acidosis. To avoid such tissue hypoperfusion, a new therapeutic strategy using vasodilators that recruit microcirculation has been proposed [1]. Levosimendan is a new drug that has vasodilator properties through stimulation of ATP-sensitive potassium channels in vascular smooth muscle cells in addition to calcium-sensitizing inotropic effects. It has been shown to improve systemic and intestinal oxygen transport [2,3]. The goal of this study was to determine whether levosimendan could improve intestinal oxygen delivery, thus avoiding elevations of intramucosal–arterial PCO_2 difference (ΔPCO_2) and preventing intramucosal acidosis without having systemic hypotensive effects in an experimental septic shock model. The effects of levosimendan were compared with those of dobutamine, an inotropic drug commonly used in treatment of septic shock.

Nineteen anesthetized, mechanically ventilated sheep were infused with *Escherichia coli* lipopolysaccharide (LPS) and immediately randomly assigned to receive either dobutamine infusion (10 μg/kg/min), levosimendan infusion (100 μg/kg/min), or saline (control group) for 2 h. A tonometer was inserted to measure intramucosal PCO_2 levels. Fluid challenge with saline was similar in all groups. In this non-lethal septic shock model, LPS infusion resulted in decreased intestinal blood flow and cardiac output associated with decreased systemic and intestinal oxygen delivery (DO_2) and increased arterial lactate level and ΔPCO_2. Dobutamine maintained cardiac output and preserved systemic DO_2, but decreased intestinal blood flow and DO_2 with an increase of ΔPCO_2. Levosimendan was found to maintain both cardiac output and intestinal blood flow with associated preservation of systemic and intestinal DO_2; this precluded the elevation of ΔPCO_2. Dobutamine and levosimendan failed to decrease arterial lactate levels. Both drugs diminished systemic and pulmonary vascular resistances and increased heart rate. As stroke volume did not change in both dobutamine and levosimendan groups, the beneficial effects of these drugs on maintaining cardiac output may be explained by induced tachycardia, as previously reported in the literature [4]. Hemodynamic effects must take into account the fact that fluid challenge in this model is relatively low, such that a relative hypovolemia may exist.

This study highlighted that levosimendan alone was able to prevent the reduction in intestinal blood flow and diminish the development of intramucosal acidosis. However, this was observed in a non-lethal septic shock model, and the study design used a short-term endotoxin infusion followed by a short-term drug infusion administered after the endotoxin challenge. This is quite different to the clinical setting. Intra-abdominal pressure was not measured in this model, although the existence of intra-abdominal hypertension may affect intestinal blood flow. In spite of this limitation, this study demonstrated that levosimendan increased intestinal blood flow with reduced intramucosal acidosis and corrected pulmonary hypertension. Further clinical trials are needed to determine the place of levosimendan in the therapeutic strategy in sepsis.

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Address for reprints: A Dubin, Universidad Nacional de La Plata, Cátedra de Farmacología, Facultad de Ciencias Médicas, 42 No 577, 1900 La Plata, Argentina. Email: arnaldodubin@speedy.com.ar

Attenuation of capillary leakage by hydroxyethyl starch (130/0.42) in a porcine model of septic shock

Marx G, Pedder S, Smith L et al.
Crit Care Med 2006;**34**:3005–10.

In the porcine model of septic shock described in this article, 6% hydroxyethyl starch (HES) of a lower molecular weight and molar substitution (HES 130/0.42) slightly improved sepsis-induced capillary leakage compared with 6% HES 200/0.5.

Fluids are a key element in the resuscitation of patients in septic shock, particularly in its early phase. There is still

considerable debate regarding the ideal fluid to use. Crystalloids are inexpensive, but rapidly disappear from the circulation and promote interstitial edema. Colloids, at least theoretically, remain in the vascular space for longer. However, endothelial permeability is increased in sepsis, and thus the volume expansion effectively achieved with colloids may be limited. The present authors investigated the effects of two hydroxyethyl starch (HES) solutions of distinct molecular weights and molar substitutions on hemodynamic and blood gas variables, and on endothelial permeability.

Fourteen pigs were randomized to a non-septic control group (n=4), or to fecal peritonitis (induced by feces spillover in the peritoneal cavity) and fluid resuscitation with 6% HES 200/0.5 (n=5) or 6% HES 130/0.42 (n=5). HES administration was guided based on the requirement to maintain central venous pressure (CVP) at 12 mmHg. Hemodynamic measurements were obtained with a pulmonary artery catheter and by extravascular lung water assessment using a double indicator dilution system (COLD system, Pulsion Medical Systems, Munich, Germany). Plasma volume was measured with chromium-51-labeled red blood cells, and albumin escape rate was assessed using iodine-125-labeled albumin. Colloid oncotic pressure was measured with an oncometer.

Mean arterial pressure was better preserved in pigs that received HES 130/0.42 than in those that were administered HES 200/0.5, even though CVP, intrathoracic blood volume, and weight gain were similar. Oncotic pressure was similar in the three groups. Plasma volume was similarly maintained with both HES solutions. The albumin escape rate was significantly higher in both septic groups than in controls, but was slightly higher with HES 200/0.5 compared with HES 130/0.42 (45% vs. 38%; $p \leq 0.05$).

The authors proposed several mechanisms to explain these differences: slightly differing pharmacological properties (less accumulation of HES in tissues with 130/0.42), distinct anti-inflammatory properties, or different microvascular effects.

The study had several limitations. Firstly, the authors compared the effects of two HES solutions in septic conditions with their effects in non-septic patients. Unfortunately, they did not include a true septic control group resuscitated with crystalloids, or a colloid control group resuscitated with albumin. The only conclusion that can be drawn is that HES 130/0.42 was associated with less capillary leakage than HES 200/0.5, which could represent either a beneficial effect of HES 130/0.42 or a detrimental effect of 200/0.5, and whether the two HES solutions are better or worse than crystalloids or natural colloids remains unclear. Secondly, the study groups included only four or five animals; hence, individual variations in septic response may account for some of the differences. Thirdly, fluid resuscitation was guided according to CVP, but was perhaps insufficient, as the animals reached a normodynamic but not a hyperdynamic state. Higher amounts of HES may have induced different effects. Finally, the changes in permeability were not associated with changes in extravascular lung water or oxygenation, even though the lungs are one of the organs most sensitive to the effects of capillary leakage.

In conclusion, HES 130/0.42 slightly improved sepsis-induced capillary leakage compared with HES 200/0.5, although this effect was not translated into significant differences in oxygenation or extravascular lung water.

Address for reprints: G Marx, Department of Anesthesiology and Intensive Care Medicine, Friedrich-Schiller University of Jena, 07737 Jena, Germany.

Inhaled nitric oxide increases endothelial permeability in *Pseudomonas aeruginosa* pneumonia

Ader F, Le Berre R, Lancel S et al.
Intensive Care Med 2007;**33**:503–10.

Inhaled nitric oxide (NO) is extensively used in intensive care units even if no survival benefit has been proved. The mechanisms of action of NO in acute lung injury (ALI) are complex. In this *Pseudomonas aeruginosa*-induced ALI model, inhaled NO did not influence lung liquid movements or the inflammatory response, but did increase endothelial permeability. This study failed to identify the mechanism responsible for this endothelial alteration, but involvement of reactive oxygen and nitrogen species cannot be ruled out.

Pseudomonas aeruginosa is the most common bacteria involved in nosocomial pneumonia. This may potentially lead to acute respiratory distress syndrome (ARDS). ARDS treatment is based on obtaining an adequate arterial oxygenation, which can be achieved by introducing inhaled nitric oxide (NO). Inhaled NO is extensively used in intensive care units even if no survival benefit has been proven. Beneficial effects of inhaled NO include modulation of pulmonary vascular tone reducing ventilation/perfusion mismatching. Along with these beneficial effects, inhaled NO induces harmful effects such as enhancement of oxidant injury by generating reactive oxygen and nitrogen species, which may damage lung epithelial cells, thus impairing gas exchange. However, the effects of inhaled NO in *P aeruginosa*-induced pneumonia have not been extensively studied.

In this experimental study, after intratracheal instillation of *P aeruginosa* mimicking acute lung injury (ALI), mechanically ventilated rats were exposed to 10 parts per million of NO with 100% oxygen fraction for 24 h. This

model is characterized by increased distal alveolar fluid clearance (DAFC) defined as an increase in the total protein concentration of the final alveolar sample compared with the initial sample. This is associated with increased epithelial and endothelial alveolar capillary permeability measured by using a ^{125}iodine-labeled albumin tracer. Inhaled NO had no influence on DAFC or epithelial permeability, but altered the endothelial barrier with increased endothelial permeability. This was not associated with an increase of NO-related products in the bronchoalveolar lavage fluid or an increase of the alveolar inflammatory response assessed by tumor necrosis factor-α, interleukin-6 (IL-6), and IL-10 levels, and neutrophil alveolar infiltration.

The authors concluded that inhaled NO did not influence lung liquid movements or the inflammatory response in this *P aeruginosa*-induced ALI model, but increased endothelial permeability. This endothelial alteration was not explained by an increase in NO products; however, a role for these cannot be ruled out. This model has some limitations, including the short-term NO exposure, whereas patients are exposed for a much longer time in the clinical setting. Oxygen was delivered at a high fraction, commonly used in the clinical setting. Its association with NO may produce toxic oxygen and nitrogen species with a potential deleterious effect on the endothelial barrier, even if this model failed to prove it. The authors did not evaluate lung blood flow, which might be influenced by inhaled NO interfering with lung fluid movement.

Address for reprints: BP Guery, Hôpital Calmette, Service de Gestion du Risque Infectieux, Pavillon Christiaens, CHRU Lille, 59037 Lille Cedex, France. Email: bguery@invivo.edu

Dose-related effects of direct hemoperfusion using a cytokine absorbent column for the treatment of experimental endoxemia

Taniuchi T, Kurita A, Mukawa C et al.
Intensive Care Med 2007;**33**:529–33.

In a rat model of endotoxic shock, these investigators found that hemoperfusion on an absorbent cartridge prevented a decrease in blood pressure and release of tumor necrosis factor-α and interleukin-6 in a dose-dependent manner. This was associated with a dose-dependent improvement in short-term outcome.

Several options are available for minimizing the impact of activation of inflammation in sepsis, including specific and non-specific pharmacological interventions and the use of external devices in order to decrease cytokine levels. The use of hemoperfusion on absorbent cartridges is one of the latter solutions. In this study, the authors evaluated the dose-related hemodynamic and anti-inflammatory effects of hemoperfusion.

A newly developed cytokine-absorbent cartridge composed of porous cellulose beds to which a hydrophobic organic compound with hexadecyl alkyl chain had been bound to the surface was used in the study. The cartridge acts as a ligand for various cytokines.

A total of 48 anesthetized and mechanically ventilated rats were injected with E coli endotoxin (15 mg/kg in 2 min), and were randomized 15 min later to a control column (of similar volume to the cartridge) or hemoperfusion on the cartridge at one of three differing active exchange volumes (0.25, 0.5, or 1 mL absorbent volume) for 120 min. In all groups, heparin was used as an anticoagulant. Temperature was kept constant in the four groups. Heart rate and arterial pressure were recorded at baseline and at 2, 4, 6, and 8 h. At similar intervals, blood samples were obtained for blood gas analysis and for determination of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) levels.

Hemoperfusion decreased the 8-h mortality rate in a dose-dependent manner (from 92% in control subjects to 58%, 42%, and 17% in the 0.25, 0.5, and 1 mL volume exchange cartridge groups, respectively). Although there was no difference in arterial pressure between groups at baseline, hemoperfusion on the cartridge blunted the reduction in arterial pressure in a dose-dependent manner. Heart rate remained stable in the four groups. Hemoperfusion blunted TNF-α peak concentration in a dose-dependent manner, but these levels returned to normal in the four groups at 4 h. In contrast, hemoperfusion blunted the increase in IL-6 level (in a dose-dependent manner), but the effect was maintained over time. Arterial pH was better preserved in half- and full-dose hemoperfusion, but there was no effect on gas exchange.

This study had several limitations. Firstly, the cartridge may have absorbed endotoxin as well as cytokines, thus limiting the insult rather than counterbalancing its effects. Although the authors could not exclude this effect by measuring endotoxin levels, they stated that it was unlikely, based on preliminary experiments not reported in the current article. Secondly, the impact of animals dying on hemodynamic variables and the cytokine profile cannot be excluded, as analysis in survivors only was not feasible in this small series of animals. Nevertheless, the trends in the various variables were already observed well before survival curves began to dissociate. Finally, these results in small animals need to be confirmed in large animals and over a longer observation period.

Regardless of the described limitations, these are promising results suggesting that hemoperfusion on this specific cartridge

can decrease the hemodynamic consequences and activation of inflammation in this rodent model of endotoxic shock.

Address for reprints: T Taniguchi, Graduate School of Medical Science, Kanazawa University, Department of Emergency and Critical Care Medicine, 13-1 Takara-machi, Kanazawa 920-8641, Japan.
Email: takutaniyan@yahoo.co.jp

RESEARCH

Economic implications of an evidence-based sepsis protocol: can we improve outcomes and lower costs?

Shorr AF, Micek ST, Jackson WL Jr et al.
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This study demonstrated that implementation of a protocol, based on the guidelines of the Surviving Sepsis Campaign, can significantly reduce overall hospital costs, in addition to reducing patient mortality rate.

The authors of the present article assessed the cost impact of implementing a multifaceted sepsis protocol in the Barnes-Jewish Hospital, St Louis, MO, USA. The "before-and-after" study was undertaken from December 2004 to November 2005, with the sepsis protocol – based on the guidelines of the Surviving Sepsis Campaign [1] – instituted in the hospital in July 2005.

The primary endpoint of the study was total hospital costs. Length of stay in hospital was a secondary endpoint. A Cox proportional hazards model was developed to correct for differences in the pre- and post-protocol implementation populations, in order to determine the independent impact of the protocol on total costs.

A total of 120 patients (mean age 64.7 years, median Acute Physiology and Chronic Health Evaluation II [APACHE II] score 22.5) were studied, with equal numbers assessed during the pre- and post-protocol periods. There were no significant differences in baseline characteristics of the two groups of patients (age, sex, race, source of infection, or severity of illness based on APACHE II score). The survival rate after implementation of the protocol was significantly higher than that prior to use of the protocol (70% vs. 52%; p=0.04).

The initial cost of implementation of the protocol, including nurse educator time, was US$5000. The median per-patient costs were significantly lower after protocol implementation (US$16 103 vs. US$21 985; p=0.008). The overall cost difference between the two groups was calculated to be US$573 000. Analysis of survivors only did not have a significant impact on the cost savings. Differences in intensive care unit and ward bed day costs were important contributors to this reduction in cost. The length of stay in hospital was significantly reduced post-protocol implementation (8 days, range 2–35 days vs. 13 days, range 3–37 days pre-protocol; p=0.001).

These data demonstrate that implementation of a protocol based on multiple interventions can result in substantial cost savings, in addition to having beneficial effects in terms of patient survival rates.

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Address for reprints: AF Shorr, The Pulmonary and Critical Care Medicine Section, Washington Hospital Center, 110 Irving Street NW, Washington, DC 20010, USA. Email: afshorr@dnamail.com

The effect of iNOS deletion on hepatic gluconeogenesis in hyperdynamic murine septic shock

Albuszies G, Vogt J, Wachter U et al.
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The authors of this study showed that inducible nitric oxide synthase is implicated in sepsis-related altered hepatic glucose production. These alterations appear to be independent of any alterations in liver perfusion.

Nitric oxide (NO) had been implicated in many pathophysiological and regulatory mechanisms in sepsis. The present authors investigated whether NO is implicated in the altered hepatic glucose production seen in sepsis.

In normal conditions, the administration of adrenergic agents is associated with an increase in endogenous glucose production, which occurs in the liver. In septic shock, liver metabolism is impaired and this alteration in liver function is accompanied by a blunted metabolic response to the adrenergic agent. This phenomenon seems to be relatively independent from liver perfusion, as it also occurs in situations where liver blood flow is maintained.

To investigate the role of NO, the authors evaluated the impact of inducible NO synthase (iNOS), by genetic deletion or by pharmacological blockade, in a murine model of long-term septic shock.

Wild-type and iNOS knockout mice were submitted to cecal ligation and perforation, and fluids and norepinephrine were administered in order to maintain liver perfusion. Wild-type mice were randomized to vehicle or selective iNOS inhibition with GW274150 (5 mg/kg intraperitoneally immediately after peritonitis induction). Mean arterial pressure, cardiac output, superior mesenteric artery blood flow and liver microvascular perfusion (laser Doppler), and oxygenation were measured every 6 h for 24 h. Hepatic glucose synthesis was measured using stable glucose isotopes and the activity of two key regulatory enzymes of glucose production, phospho-

enolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G-6-P), was measured spectrophotometrically. Nitrite and nitrate levels were also determined.

Mean arterial pressure was maintained similarly in the three groups. Cardiac output and superior mesenteric blood flow were stable in the three groups, but were higher in the vehicle-treated control mice than in the iNOS-deficient or inhibitor-treated mice. Liver microvascular perfusion and oxygen saturation remained stable and similar in the three groups. Glucose production was higher (almost double) in both animals deficient for iNOS and inhibitor-treated mice compared with control animals. PEPCK activity was slightly but significantly higher in both iNOS-deficient and -blocked groups than in controls, while G-6-P activity was similar in the three groups. Nitrite and nitrates were markedly decreased in iNOS-knockout but not in iNOS-blockade mice. Together, these data highlight the role of the NO pathway, specifically iNOS, in the altered hepatic glucose production in sepsis.

The clinical implications of these results are difficult to determine, as the role of iNOS in other alterations in liver metabolic pathways during sepsis cannot be inferred from these data.

One important limitation of this study is that microvascular perfusion and oxygenation were grossly evaluated, as the technique of measurement did not take into account perfusion heterogeneity. Importantly, hepatic glucose production is a highly oxygen (O_2)-consuming process; thus, it is intriguing that liver O_2 consumption was apparently stable (microvascular blood flow, O_2 saturation, and hemoglobin levels were stable and similar in the three groups) while hepatic glucose production doubled. If correct, this would imply that other O_2-consuming liver metabolic pathways were switched off during iNOS blockade or deletion. Despite this limitation, these data add some important insights into the pathophysiology of liver metabolic alterations.

Address for reprints: P Radermacher, Universitätsklinikum, Sektion Anästhesiologische Pathophysiologie und Verfahrensentwicklung, Parkstrasse 11, 89073 Ulm, Germany. Email: peter.radermacher@uni-ulm.de

Adrenomedullin reduces vascular hyperpermeablity and improves survival in rat septic shock

Temmesfeld-Wollbrück B, Brell B, Dávid I et al.
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In this study, administration of adrenomedullin, an endogenous peptide described to be elevated in sepsis, improved outcome, hemodynamics and vascular permeability in a rat model of sepsis induced by ingestion of *Staphylococcus aureus* α-toxin. The exact mechanisms underlying these effects have not been determined.

Adrenomedullin is an endogenous peptide that has been shown to be elevated in sepsis. In addition to possessing anti-inflammatory and anti-apoptotic properties, adrenomedullin improves hemodynamic stability in experimental models of sepsis. The precise mechanisms behind this remain unclear. In particular, the role of adrenomedullin on myocardial function is unknown, as the improved hemodynamic stability may represent either a direct effect or a decrease in afterload related to its vasodilator properties. In addition, adrenomedullin may limit the increase in vascular permeability seen in sepsis, reflecting better preserved endothelial function.

In this article, the authors evaluated the hemodynamic effects of adrenomedullin and its impact on vascular permeability in control and septic conditions. Sepsis was induced by *Staphylococcus aureus* α-toxin, in order to explore mechanisms not related to endotoxin or Gram-negative infections.

Male rats were anesthetized and mechanically ventilated. Mean arterial pressure was measured invasively and cardiac output was measured using transpulmonary thermodilution. Rats were allocated to four groups: control groups with or without adrenomedullin (24 μg/kg/h via a tail vein) and sepsis groups with or without adrenomedullin (4800 U/kg *S aureus* α-toxin through a central venous catheter over 45 min). Adrenomedullin was started 1 h after *S aureus* α-toxin administration. Fluids were administered at a rate of 12 mL/kg/h with additional volume to compensate for blood sampling.

Hemodynamic measurements were obtained hourly for 6 h. Vascular permeability was measured at 6 h or when mean arterial pressure dropped below 40 mmHg in dying animals. Vascular permeability was measured in lungs, liver, ileum and kidneys using Evans blue dye-linked albumin injection and determination of Evans blue dye content of these organs at histology (organs were harvested 15 min after dye administration).

Adrenomedullin reduced the mortality rate: 50% of non-treated septic animals died within 6 h of observation, while only one septic animal treated with adrenomedullin died within this period. None of the control animals died.

In control animals, adrenomedullin slightly decreased blood pressure (by approximately 15%) while it markedly increased cardiac index (by 60%). In non-treated septic animals, blood pressure and cardiac index markedly decreased (by approximately 50% and 40%, respectively). These effects were minimized by adrenomedullin; in septic animals treated with adrenomedullin, arterial pressure decreased by 25% while cardiac index increased by 15%.

While adrenomedullin had no impact on vascular permeability in control animals, vascular permeability markedly increased in all organs in septic animals and this

increase was prevented by adrenomedullin administration. In addition, in non-treated septic animals, there was a redistribution of dye from the cortex to the medulla and this effect was also inhibited by adrenomedullin. There was a negative correlation between changes in arterial pressure and increased permeability.

As shown in control conditions, adrenomedullin is associated with intrinsic hemodynamic properties. However, it is difficult to ascertain whether the beneficial effects of adrenomedullin in septic conditions were related to the improved hemodynamics or to other effects.

One of the most important limitations of the study is that the investigators were unable to separate measurements from non-surviving and surviving animals in the non-treated septic group due to the small number of animals in each group. Accordingly, measurements of agonic animals were combined with measurements from surviving animals, thus differing from the adrenomedullin-treated group in which all animals survived to the time of measurement. Therefore, some of the effects (hemodynamic as well as the impact on vascular permeability) were perhaps not directly related to adrenomedullin, but indirectly reflected a blunted response to α-toxin. Investigating the response of surviving animals only would have allowed conclusive assessment of a direct effect.

In summary, adrenomedullin improved outcome, hemodynamics, and vascular permeability. The exact mechanisms underlying these effects remain to be determined.

Address for reprints: S Hippenstiel, Charité–University Medicine Berlin, Department of Internal Medicine/Infectious Diseases and Respiratory Medicine, Augustenburger Platz 1, 13353 Berlin, Germany.
Email: stefan.hippenstiel@charite.de

Engineering a disulfide bond to stabilize the calcium-binding loop of Activated Protein C eliminates its anticoagulant but not its protective signaling properties

Bae JS, Yang L, Manithody C et al.
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The authors of this study demonstrated that a Cys^{67}–Cys^{82} protein C mutant may offer the advantage of preserved anti-apoptotic, anti-inflammatory, and anti-adhesion effects, without any anticoagulant activity.

The two endothelial cell surface receptors, endothelial protein C receptor (EPCR) and thrombomodulin (TM), enhance the activation of protein C by thrombin by three- to four-fold, in a calcium-dependent manner. The binding of calcium to the 70–80 loop of protein C is required for recognition of the protein by the thrombin–TM complex and for its anticoagulant activity. Mutants of protein C with a disulfide bond between cysteine-67 (Cys^{67}) and Cys^{82}, which stabilizes this calcium-binding loop, have been generated in mutagenesis studies.

The present authors evaluated the anticoagulant and anti-inflammatory properties of Cys^{67}–Cys^{82} activated protein C (APC). All studies were performed using cell cultures of a transformed human endothelial cell line and freshly isolated white blood cells. Protein C activation by thrombin was evaluated in the absence and presence of calcium and TM. Endothelial permeability was evaluated on endothelial cell cultures, measuring the flux of Evans blue dye-bound albumin, after activation by thrombin. Apoptosis of endothelial cells (evaluated by the terminal transferase dUTP nick end labeling [TUNEL] assay) was induced by staurosporine. Adhesion of white blood cells to endothelial cells was evaluated in the presence of an adhesion medium. All these experiments were conducted in the absence or presence of APC (either wild-type or mutant).

The activation of mutant APC by thrombin was enhanced 60–80-fold compared with the native form, independently of the presence of TM or calcium. Addition of TM failed to further accelerate protein C activation. The anticoagulant activity of the mutant was dramatically impaired, as it almost failed to affect clotting time. The binding of Cys^{67}–Cys^{82} APC to the EPCR receptor was preserved. Cys^{67}–Cys^{82} APC and wild-type APC similarly blunted the thrombin-increased endothelial permeability, with both forms requiring the presence of a functional EPCR and protease-activated receptor-1 (PAR-1). Cys^{67}–Cys^{82} APC and wild-type APC also similarly blunted staurosporine-induced apoptosis, white blood cell migration, and adhesion molecule expression in the presence of an adhesion medium.

In conclusion, the Cys^{67}–Cys^{82} APC mutant has similar effects to native APC on adhesion and apoptosis (with both effects being mediated by EPCR and PAR-1), while its anticoagulant properties are minimized. The generation of this APC mutant opens the way for investigation of the respective contribution of anticoagulation and other properties of APC to its protective effects in sepsis.

Address for reprints: A Rezaie, Department of Biochemistry and Molecular Biology, Saint Louis University School of Medicine, 1402 South Grand Boulevard, St Louis, MO 63104, USA.
Email: rezaiear@slu.ed

MEETING REPORT

36th Critical Care Congress of the Society of Critical Care Medicine (SCCM)

Orlando, FL, USA, 17–21 February 2007

Timothy D Girard, MD, MSCI

Department of Medicine, Division of Allergy, Pulmonary, and Critical Care Medicine and Center for Health Services Research, Vanderbilt University School of Medicine, Nashville, TN, USA

The Society of Critical Care Medicine (SCCM) hosted its 36th Critical Care Congress in Orlando, FL, USA, in February, and sepsis was a focal point of numerous research and educational presentations. With more than 5000 critical care specialists – including nurses, respiratory therapists, pharmacists, physicians, and other scientists – participating, the Congress was a tremendous success. This meeting report highlights several of the outstanding sepsis-related presentations. Many other important sepsis research projects that are not covered in this report are presented in abstract form in the December 2006 supplement of the *Critical Care Medicine* journal [1].

Delivering care using sepsis protocols

During the past decade, several clinical trials have demonstrated the efficacy of new sepsis therapies, but translating evidence into clinical practice is often a slow and cumbersome process. To promote this transition, the Surviving Sepsis Campaign (SSC) recommends the use of severe sepsis bundles, i.e. groups of sepsis-related interventions that result in better outcomes when implemented together than when implemented individually [2]. The evidence supporting the use of sepsis protocols, often based on sepsis bundles, was reviewed in a session entitled "Integrated Sepsis Protocols".

Sean Townsend (Brown University School of Medicine, Providence, RI, USA), a member of the SSC Executive Committee, emphasized the vital role that evidence-based sepsis protocols can play in a medical system that often fails to deliver recommended care [3]. After describing the bundle concept, Dr Townsend reviewed the results of a prospective study by Gao et al., which found that compliance with sepsis bundles during the management of 101 adult medical and surgical patients with severe sepsis or septic shock was associated with lower in-hospital mortality [4]. The SSC recommends that hospitals use the 6-h and 24-h sepsis bundles to create customized protocols.

In another example, Nathan Shapiro (Beth Israel Deaconess Medical Center, Boston, MA, USA) reported the effect of an emergency department-based sepsis protocol named the Multiple Urgent Sepsis Therapies (MUST) protocol [5], which resulted in septic patients receiving more intravenous fluid, earlier antibiotics with more appropriate empirical coverage, more vasopressors, tighter glucose control, and more frequent assessment of adrenal function. The success of the MUST protocol was dependent upon a six-step process: admitting the need to improve care, collaboration by multiple departments, organization of the protocol, education of care givers, implementation of the protocol, and evaluation using quality assurance measures and benchmarks. Following these steps helped to overcome barriers to implementation that were described by other speakers during this session.

The economic implications of sepsis protocols were studied by Andrew Shorr (George Washington University, Washington, DC, USA) and colleagues, who compared total hospital costs for 60 patients managed with a sepsis protocol in the emergency department of a tertiary care medical center with those for 60 patients managed prior to implementation of the sepsis protocol [6]. Despite a greater number of survivors in the protocol-managed group, total costs were US$573 000 lower compared with the group managed without the protocol. In fact, after adjusting for age, gender, race, and infection source, receipt of the protocol was associated with a cost reduction of US$7049 per patient, primarily due to a reduction in intensive care unit (ICU) length of stay.

Address for correspondence: Timothy Girard, 6th Floor MCE, Suite 6110, Vanderbilt University Medical Center, Nashville, TN 37232-8300, USA. Email: timothy.girard@vanderbilt.edu

Individualized sepsis therapy

Whereas sepsis bundles and protocols are designed to treat the broad population of patients with severe sepsis, management strategies in the future may be influenced more by individual patient characteristics. Several speakers introduced the concept of individualized sepsis therapy, arguing that sepsis is not a homogeneous disease entity, but a syndrome of signs and symptoms arising from a variety of infections and associated with a range of host responses. Daniel Remick (University of Michigan, Ann Arbor, MI, USA) reported that several biomarkers, including interleukin-6 and macrophage inflammatory protein-2 can predict mortality in animal models of sepsis. Recent trials in mice indicate that sepsis therapies, such as corticosteroids, may be most effective when given to patients with a high risk of death according to cytokine concentrations.

Edward Abraham (University of Alabama at Birmingham, Birmingham, AL, USA) also promoted research that may lead to individualized sepsis therapy. Instead of continuing to search for a magic bullet designed to treat a single alteration responsible for all organ dysfunction in a septic patient, he suggested that genomics and proteomics could be used to identify specific cellular alterations associated with certain clinical presentations of sepsis. Interventions that modify these alterations could then be designed and studied as individualized therapies.

Recent randomized clinical trials

Until individualized sepsis therapy is proven and widely available, large randomized clinical trials of sepsis therapies will continue to study the efficacy and safety of unproven interventions among broad populations of septic patients. The results of several such sepsis trials were presented in the "Update on Clinical Trials in Severe Sepsis" session.

The CORTICUS (Corticosteroid Therapy of Sepsis and Septic Shock) trial [7] was recently completed, and the results were presented by Charles Sprung (Hadassah Medical Center, Jerusalem, Israel). CORTICUS enrolled 500 patients (499 were analyzed) with septic shock of <72 h, making it the largest randomized trial to evaluate the efficacy of replacement-dose steroids for septic shock, a therapy that has generated considerable controversy over the past several years. Patients in the treatment group, who received 11 days of hydrocortisone (50 mg every 6 h for 5 days, then less frequently) had similar 28-day mortality rates to those patients treated with placebo (33.5% vs. 31%; p=0.57). Thus, steroids cannot be recommended for the broad population of older patients with septic shock.

All CORTICUS patients underwent an adrenocorticotropic hormone (ACTH) stimulation test, since an earlier trial suggested that replacement-dose steroids are most beneficial for septic shock patients with adrenal insufficiency [8]. Subgroup analysis of those with adrenal insufficiency (i.e. ACTH nonresponders) revealed a higher mortality rate among such patients compared with ACTH responders, but treatment with hydrocortisone had no effect on 28-day mortality rate in the ACTH nonresponders (37.6% in those treated with hydrocortisone vs. 35.2% in those treated with placebo; p=0.79). Regardless of ACTH responsiveness, treatment with hydrocortisone led to earlier reversal of shock (p=0.003), but this advantage may have been offset by superinfection (34% in patients treated with hydrocortisone vs. 27% in patients treated with placebo; p=0.10).

The results of the LIPOS (Lipid Infusion and Patient Outcomes in Sepsis) trial were presented next by R Phillip Dellinger (Cooper Health System, Camden, NJ, USA), another member of the SSC Executive Committee. In LIPOS, 1379 patients with Gram-negative severe sepsis were randomized to treatment with placebo, low-dose, or high-dose GR270773 (GlaxoSmithKline, Brentford, Middlesex, UK), an intravenously administered lipid emulsion that consists of approximately 90% lipoprotein phospholipids, which bind and neutralize endotoxin. Despite promising results in animal models, GR270773 did not reduce 28-day mortality rate in LIPOS (26.9% in the placebo group vs. 25.8% in the low-dose GR270773 group vs. 31.3% in the high-dose GR270773 group). Anemia was the most frequently reported adverse effect in all three treatment groups, and red blood cell transfusions were required for some patients.

Djillali Annane (Raymond Poincaré University Hospital, Garches, France) concluded the session by presenting results from a recently completed trial that compared norepinephrine plus dobutamine with epinephrine alone for hemodynamic support of patients with septic shock. This multicenter, randomized, double-blind trial enrolled 330 patients who had been in septic shock <24 h to determine the effect of the two treatment regimens on 28-day mortality rate as well as organ failure, time on vasopressors, and other secondary outcomes. Blood pressure improved with treatment in both groups, and mortality, organ failure, and time on vasopressors were not significantly affected by choice of vasopressor; 28-day mortality rate was 34.3% in those treated with norepinephrine plus dobutamine versus 39.8% in those treated with epinephrine (p=0.31).

Hemodynamic support of sepsis

Another session was dedicated to the review of the evidence guiding hemodynamic support for patients with sepsis. Judith Jacobi (Clarian Health Partners, Indianapolis, IN, USA) began the session by discussing the rationales for treating

septic patients with crystalloid versus colloid versus blood. The SAFE (Saline versus Albumin Fluid Evaluation) study was the largest clinical trial to examine whether the choice of resuscitation fluid for ICU patients affects survival [9]. Of the 6997 patients enrolled in the SAFE study, 1218 had severe sepsis. Although no survival advantage was attributable to either saline or albumin among the entire study population (relative risk of death if treated with albumin instead of saline 0.99; 95% confidence interval [CI] 0.91–1.09; p=0.87), results among the subgroup with severe sepsis suggested a possible survival benefit favoring treatment with albumin (relative risk of death if treated with albumin instead of saline 0.87; 95% CI 0.74–1.02; p=0.09). The current SSC guidelines recommend either colloid or crystalloid for the initial resuscitation of patients with septic shock, and the SAFE study results are unlikely to change these recommendations [10].

The VASST (Vasopressin in Septic Shock Trial) examined the effect of hemodynamic support with low-dose vasopressin (0.03 U/min) versus norepinephrine (15 μg/min) in 799 patients with septic shock [11]. Open-label vasopressors were given as needed in addition to the vasopressin or norepinephrine determined by random assignment. As explained by James Russell (The University of British Columbia, Vancouver, BC, Canada), for the entire study population, vasopressin did not improve 28-day mortality rate compared with norepinephrine (35.4% vs. 39.3%; p=0.27). However, examination of subgroups revealed that vasopressin may be of benefit among septic patients with less severe shock: patients receiving <15 μg/min of norepinephrine at enrollment benefited from treatment with vasopressin compared with those given norepinephrine alone (28-day mortality rate 26.5% vs. 35.7%; p=0.05).

Conclusion

Although there is ongoing uncertainty regarding many aspects of the care of critically ill patients with sepsis – as evidenced by the lively debates on the use of corticosteroids, vasopressin, and early goal-directed therapy in the "International Sepsis Forum (ISF): Controversies in Sepsis" session – research in this area continues to provide guidance to practitioners and to ultimately improve the outcomes of patients with sepsis. The SCCM's 36th Critical Care Congress proved to be an exciting forum for the dissemination of much of the latest sepsis research, covering a broad range of sepsis-related studies. The 37th Critical Care Congress, which will be held on February 2–6, 2008, on the beautiful island of Oahu, HI, USA, promises to advance even further the Society's commitment to educate critical care practitioners and promote critical care research.

Disclosures

The author has honararia from Hospira, Inc.

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