LEADING ARTICLE

Drugs 1999 Feb; 57 (2): 127-132
0012-6667/99/0002-0127/$06.00/0



# Treatment of Sepsis
## Past and Future Avenues

*Jean-Daniel Baumgartner*[1] and *Thierry Calandra*[2]

1 Service of Internal Medicine, Hôpital de Zone, Morges, Switzerland
2 Division of Infectious Diseases, Department of Internal Medicine, Center Hospitalier Universitaire Vaudois, Lausanne, Switzerland

**Abstract**

In recent years, the concept has emerged that the host's inflammatory response contributes substantially to the development of septic shock and organ failure. Experimental observations prompted large scale randomised clinical trials with a variety of agents such as glucocorticoids, ibuprofen, antiendotoxin monoclonal antibodies, antagonists of platelet-activating factor, of bradykinin or of interleukin-1 receptor, and monoclonal anti–tumour necrosis factor (TNF) antibodies or soluble dimeric TNF receptor fusion proteins.

All these major studies of immunomodulators in sepsis have yielded disappointing results despite showing promise during preliminary clinical studies. However, these recent failures do not mean that septic shock will forever remain an insurmountable medical challenge. Many lessons have been learned from these studies. and certain mistakes in their study design will be avoided in the future. Our understanding of the pathophysiology of sepsis and septic shock is increasing markedly; potential new treatment strategies are available and could be explored to improve the outcome of patients with sepsis.

Our understanding of the pathophysiology of sepsis and septic shock has increased markedly over the past few years.[1-5] Sepsis begins when bacteria cross host barriers, overwhelming host defences, and release toxic bacterial products that activate plasma factors (complement and clotting molecules) and cells of the immune system (monocytes/macrophages, polymorphonuclear cells and lymphocytes). Cell receptors for toxic microbial products and serum factors that enhance host responses to bacterial products have been characterised. Upon activation by bacterial products, host cells release a complex array of mediators, including cytokines. Cytokines are autocrine and paracrine molecules that act locally at their site of production and serve to orchestrate the cellular and humoral host responses. By influencing coagulation and leucocyte transmigration, and by activating professional phagocytes, cytokines assist the host to contain a local infection.

However, in septic shock, this process is out of control. The synthesis of pro-inflammatory molecules, especially tumour necrosis factor (TNF) and interleukin (IL)-1, upregulates the expression of adhesion molecules on endothelial cells, promoting the accumulation of activated polymorphonuclear cells. This leads to further cytokine production and release of toxic molecules from polymorphonuclear cells, resulting in endothelial necrosis and vascular permeability. Septic shock is a manifestation of a dysregulated inflammatory response during which the counter-regulatory systems, including anti-inflammatory cytokines (IL-4, IL-10, IL-13, transforming growth factor β, granulocyte

colony–stimulating factor) soluble TNF receptors, IL-1 receptor antagonist and glucocorticoids, are overwhelmed. The pro-inflammatory response affects vascular permeability and resistance and cardiac function, and induces many metabolic derangements often leading to multiorgan failure and death.

## 1. Where Are We Now?

In recent years, the concept has thus emerged that the host's inflammatory response contributes substantially to the development of shock and organ failure. Although many experimental studies have focused on Gram-negative septic shock, we now know that endotoxin is not the universal trigger of septic shock that it was once believed to be. Gram-positive bacteria also can cause a clinical syndrome that is similar to Gram-negative septic shock, but the cellular and molecular mechanisms of Gram-positive shock have not been fully elucidated. Systemic fungal infections can also produce sepsis and septic shock, yet the pathophysiology of fungal sepsis remains largely unknown.

The current strategies of adjunctive therapy for sepsis are mainly derived from observations made in animal models. Promising experimental results prompted large scale randomised clinical trials with a variety of agents such as antiendotoxin (anti-lipid A) monoclonal antibodies,[6-9] glucocorticoids[10,11] or ibuprofen[12] for nonspecific down-regulation of inflammation, antagonists of platelet activating factor,[13,14] of bradykinin[15] or of IL-1 receptor,[16,17] and monoclonal anti-TNF antibodies[18-21] or soluble dimeric TNF receptor fusion proteins.[22,23] Unfortunately, despite some promising results during preliminary trials, all the major clinical studies of immunomodulators in sepsis have yielded disappointing results (for discussion see, for example, Bone,[24] Abraham and Raffin[25] and Zeni et al.[26]). A phase III study of a p55 TNF receptor IgG1 fusion protein was recently terminated after inclusion of 1342 patients. The preliminary results showed no difference in the 28-day mortality rates between the patients receiving the fusion protein and placebo, respectively. Analysis of subgroups showed that no subgroup showed convincing benefit (E. Abraham, personal communication).

There are several explanations for the discordant results observed between animal models and in clinical trials. Major differences exist between animal models of sepsis and clinical septic shock. In animal models, the cascade of events is perfectly synchronised and follows a predictable and brief course usually ranging from a few hours to a few days. The initial stimulus is usually given as a single, titrated dose, via the same route, to healthy animals with the same genetic background. The infections or toxic challenges are accompanied by the release of a transient and usually single burst of each cytokine. Experimental protocols aimed at blocking a single cytokine cascade are thus relatively straightforward. In animal models, cytokine blockade is efficient only when performed prophylactically or very early after challenge, which is obviously not feasible in humans.

In contrast, the sequence of events leading to septic shock in humans is much more complex, asynchronised, and extends over a prolonged period of time, usually many days. Therefore, immunological interventions have to work in a very complex environment in which opposing pro- and anti-inflammatory forces are in action. In fact, in late shock, it might even be that the pro-inflammatory burst is over and that the patient is in a state of hyporesponsiveness which would require stimulation rather than inhibition.

Furthermore, the design of the clinical trials themselves raises several unresolved issues, such as the criteria used for the selection of the endpoints (for example, mortality versus morbidity, all-cause death versus death due to septic shock only, 28-day mortality versus early mortality), and the existence of confounding factors (for example, decision not to resuscitate, inadequacy of treatment, underlying diseases).

However, perhaps the major issue is the selection of patients. Indeed, in all recent clinical trials, the selection of patients was based on the sepsis criteria proposed by Bone et al.,[27] a method that

has been criticised.[28] The concept of sepsis syndrome relies on the belief that the pathophysiology of sepsis and organ dysfunction is similar whatever the microbial aetiology and primary focus of infection may be. However, there are 2 major problems with this concept. First, the systemic manifestations of infection that can be readily recorded are highly nonspecific and can also occur with many noninfectious illnesses. Secondly, the assumption that the pathophysiology of sepsis is similar for all micro-organisms and primary foci of infections is doubtful. The concept of sepsis syndrome became very popular because it allows the inclusion of a substantial number of intensive care unit patients in clinical trials, allowing the performance of the large-scale randomised trials that are required for statistical reasons. However, the power of these studies was lower than expected because the selection of patients was based on the nonspecific criteria of the sepsis syndrome.

Although the clinical studies performed so far have not allowed the conclusion that, for instance, TNF or IL-1 blockade is effective in patients with sepsis or septic shock, we do not yet really know whether these agents have some protective efficacy or not. Future clinical trials in this field should have carefully designed entry criteria no longer based on the single concept of sepsis syndrome. These trials should also select more homogenous patient populations, such as for example those with intra-abdominal infections, nosocomial pneumonia or fulminant meningococcaemia. Timing of intervention is also crucial. In fact, in the recently completed anti–TNF multicentre studies,[23,29,30] only a small proportion of the patients had detectable circulating TNF levels at entry, raising the possibility that treatment might have been administered too late, after peak TNF release in the blood. This stresses the need for laboratory tests to help clinicians identify at the bedside those patients who are likely to benefit from the experimental drug.

## 2. Where Do We Go?

The fact that all recent clinical trials of anti-inflammatory agents have yielded disappointing results does not mean that septic shock will forever remain an insurmountable medical challenge. Many lessons have been learned from previous studies and the failure of the current approaches should stimulate researchers to find new treatment modalities. As shown in table I, many strategies are available to interrupt the cascade of events that occurs during septic shock. Although some of these treatment approaches are still at a preclinical stage, others are, or will soon be, in clinical development. It is beyond the scope of this article to review all these treatment options, and therefore only some will be considered.

Despite the lack of efficacy of antiendotoxin antibodies, one approach worth pursuing is to block the ability of microbial agents to activate target cells. Candidate molecules are lipid A antagonists,[31-34] acyloxyacyl hydrolase,[34] bactericidal/permeability-increasing protein,[35] cationic antimicrobial proteins (CAP18 and 37),[36] antilipopolysaccharide factor[37] and high density lipoproteins (HDL). Lipoproteins are natural antagonists of endotoxin (lipopolysaccharide; LPS). Recently, it was found that LPS binding protein (LBP) and soluble CD14 also catalyse the transfer of LPS to HDL.[38,39] Administration of lipoproteins decreases cytokine production *in vitro* and *in vivo* and protects animals from endotoxic shock.[40-44] A phase II study of reconstituted HDL for the treatment of peritonitis will soon be initiated in Europe.

Another treatment option is to prevent the activation of responsive cells by microbial products. LBP and CD14 (both its membrane-bound and soluble forms) are 2 critical components of the activation of host cells by LPS. Recent investigations have shown that CD14 is also involved in the recognition of many other micro-organisms, including Gram-positive bacteria, mycobacteria and yeasts, and is thus an integral component of innate immunity.[45] In animal models, blockade of LBP has been shown to prevent death from shock induced by endotoxin or by Gram-negative bacteria,[46] and transgenic mice overexpressing human CD14 were found to be hypersensitive to LPS.[47] Recent experiments with LBP- or CD14-knockout

**Table I.** Present and future strategies for the treatment of patients with sepsis

| |
|---|
| **1. Blocking the release or the action of microbial products** |
| Neutralisation of lipopolysaccharide |
| lipid A antagonists |
| acyloxyacyl hydrolase |
| antilipopolysaccharide factor |
| bactericidal/permeability-increasing protein |
| cationic antimicrobial proteins |
| reconstituted high density lipoprotein |
| Neutralisation of bacterial toxins or microbial cell walls with inhibitors or antibodies |
| **2. Preventing the activation of responsive cells** |
| Blocking lipopolysaccharide–binding protein or CD14 |
| Interfering with intracellular signalling cascades |
| tyrosine kinases |
| mitogen-activated protein kinase superfamily |
| lipid mediators (phospholipases, diacylglycerols, phosphatidylinositol 3,4,5-trisphosphate, protein kinase C, sphingomyelin, ceramide) |
| Inhibiting the action of transcription factors (nuclear factor-κB, activator protein-1) |
| **3. Inhibiting secondary mediators** |
| Cytokines |
| inhibition of cytokine synthesis and release (steroids, interleukin-10, phosphodiesterase inhibitors, thalidomide, CNI-1493, inhibitors of tumour necrosis factor converting enzyme) |
| neutralisation of cytokine activity (monoclonal antibodies, soluble receptors, receptor antagonists) |
| Nitric oxide |
| specific and nonspecific inhibitors of inducible nitric oxide synthase |
| Lipid mediators |
| platelet-activating factor antagonists |
| blockade of the cyclo-oxygenase–dependent and the lipoxygenase-dependent pathways |
| **4. Blocking the activation of humoral pathways** |
| Inhibition of coagulation (antithrombin III, inhibition of tissue factor pathway) |
| Inhibition of complement |
| Inhibition of kinin (bradykinin antagonists) |
| **5. Preventing the activation of target cells** |
| Neutralisation of adhesion molecules (selectins, integrins) |
| **6. Immunostimulation** |
| Interferon-γ, granulocyte colony–stimulating factor, granulocyte-macrophage colony–stimulating factor, interleukin-12, interleukin-18 |

mice confirmed the importance of these 2 molecules in the pathophysiology of septic shock.[48,49] No data are yet available on the effect of anti-LBP or anti-CD14 antibodies in humans with sepsis.

The elucidation of the signalling pathways involved in gene expression after the activation of the cell membrane receptor by LPS or other microbial agents has been an area of intensive research in recent years. Several signalling cascades have been identified, including the mitogen-activated protein (MAP) kinase superfamily.[50] Each component of these pathways is a potential target for drug development. Small inhibitors of these signalling molecules should soon be available for testing in experimental animal models of sepsis. Further downstream targets are the transcription factors nuclear factor (NF)-κB and activator protein (AP)-1, which play a critical role in the expression of many pro-inflammatory mediators and acute phase proteins.

The inhibition of secondary mediators, such as the cytokines, nitric oxide or the lipid mediators, has been extensively studied in the last 15 years. New mediators of inflammation continue to be identified. The sequencing of the human genome will also provide scientists with many new molecules likely to be involved in the pathogenesis of septic shock; each one may be a target for novel therapies. On the other hand, old cytokines may be 'rediscovered'. For example, the biological role of macrophage migration inhibitory factor (MIF), one of the first lymphocyte cytokines described (in the late 1960s), has been uncovered recently. MIF was found to be a pro-inflammatory macrophage and pituitary mediator that plays a critical role in septic shock.[51,52] Surprisingly, MIF production is also induced by glucocorticoids and it functions as a counter-regulator of the anti-inflammatory and immunosuppressive effects of steroids on macrophages and T cells.[53,54] More recent experiments have shown that MIF plays an important role in animal models of glomerulonephritis, arthritis and allograft rejection, indicating that it is a critical mediator of acute inflammation. Anti–MIF strategies may find utility in the management of septic shock or other inflammatory diseases.

Many systems are activated during septic shock. Blocking the coagulation, complement or kinin cascades is another attractive approach for the

management of patients with sepsis. Studies using antithrombin III or inhibitors of the tissue factor pathway are currently in progress. Inhibition of the selectins or integrins is yet another potential strategy for preventing the activation of inflammatory or immune cells.

Conversely, several studies have shown that the immune cells of patients with sepsis are hyporesponsive or deactivated, suggesting that critically ill patients may be immunosuppressed, especially in the post-acute phase of septic shock.[55] These observations have led some investigators to promote an alternative strategy using agents such as interferon-γ, granulocyte colony–stimulating factor or granulocyte-macrophage colony–stimulating factor to boost immune function and reverse cellular deactivation in these patients. Preliminary data suggest that treatment with interferon-γ may improve immune function in selected medical and surgical intensive care unit patients, but double-blind placebo-controlled studies are needed to examine further the efficacy and tolerability of such interventions.[56]

## 3. Conclusions

Although the results of recent clinical trials of adjunctive therapy for sepsis have been discouraging, several potential treatment strategies are available and could be explored to improve the outcome of such patients. The success of these approaches will rely both on improvement of our scientific knowledge and ability to develop agents for clinical trials, and on improved selection of suitable patients for these trials.

## Acknowledgements

T.C. is supported by a career award from the Swiss National Science Foundation (grants 32-48916.96 and 32-49129.96).

## References

1. Heumann D, Glauser MP. Pathogenesis of sepsis. Sci Am 1994; 1: 28-37
2. Glauser MP. The inflammatory cytokines: new developments in the pathophysiology and treatment of septic shock. Drugs 1996; 52 Suppl. 2: 9-17
3. Glauser MP, Heumann D, Baumgartner JD, et al. Pathogenesis and potential strategies for prevention and treatment of septic shock: an update. Clin Infect Dis 1994; 18 Suppl. 2: S205-16
4. Natanson C, Hoffman WD, Suffredini AF, et al. Selected treatment strategies for septic shock based on proposed mechanisms of pathogenesis. Ann Intern Med 1994; 120: 771-83
5. Parrillo JE. Pathogenetic mechanisms of septic shock. N Engl J Med 1993; 328; 1471-7
6. Ziegler EJ, Fisher CJ Jr, Sprung CL, et al. Treatment of Gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin: the HA-1A study group. N Engl J Med 1991; 324: 429-36
7. McCloskey RV, Straube RC, Sanders C. Treatment of septic shock with human monoclonal antibody HA-1A: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1994; 120: 1-5
8. Greenman RL, Schein RMH, Martin MA, et al. A controlled clinical trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of gram-negative sepsis. JAMA 1991; 266: 1097-102
9. Bone RC, Balk RA, Fein AM, et al. A second large controlled clinical study of E5, a monoclonal antibody to endotoxin: results of a prospective, multicenter, randomized, clinical trial. Crit Care Med 1995: 23: 994-1006
10. Veterans Administration Systemic Sepsis Cooperative Study Group. Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. N Engl J Med 1987 ; 317: 659-65
11. Bone RC, Fisher CJ Jr, Clemmer TP, et al. A controlled clinical trial of high-dose methyl-prednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 1987; 317: 653-8
12. Bernard GR, Wheeler AP, Russell JA, et al. The effect of ibuprofen on the physiology and survival of patients with sepsis. N Engl J Med 1997; 336: 912-8
13. Dhainaut J-FA, Tenaillon A, Le Tulzo Y, et al. Platelet-activating factor receptor antagonist BN 52021 in the treatment of severe sepsis: a randomized, double-blind, placebo-controlled, multicenter clinical trial. Crit Care Med 1994; 22: 1720-8
14. Dhainaut JFA, Tenaillon A, Hemmer M, et al. Confirmatory platelet-activating factor receptor antagonist trial in patients with severe gram-negative bacterial sepsis: a phase III, randomized, double-blind, placebo-controlled multicenter trial. BN 52021 Sepsis Investigator Group. Crit Care Med 1998; 26: 1963-71
15. Fein AM, Bernard GR, Griner GJ, et al. Treatment of severe systemic inflammatory response syndrome and sepsis with a novel bradykinin antagonist, deltibant (CP-0127): results of a randomized, double-blind, placebo-controlled trial. JAMA 1997; 277: 482-7
16. Fisher CJ Jr, Dhainaut J-FA, Opal SM, et al. Recombinant human interleukin-1 receptor antagonist in the treatment of patients with sepsis syndrome: results of a randomized, double-blind, placebo-controlled trial. JAMA 1994; 271: 1836-43
17. Opal SM, Fisher CJ Jr, Dhainaut J-FA, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. Crit Care Med 1997; 25: 1115-24
18. Reinhart K, Wiegand-Lohnert C, Grimminger F, et al. Assessment of the safety and efficacy of the monoclonal anti-tumor necrosis factor antibody fragment, MAK 195F, in patients with sepsis and septic shock: a multicenter, randomized, placebo-controlled, dose-ranging study. Crit Care Med 1996; 24: 733-42
19. Abraham E, Wunderink R, Silverman H, et al. Efficacy and safety of monoclonal antibody to human tumor necrosis factor-alpha in patients with sepsis syndrome: a randomized,

controlled, double-blind, multicenter clinical trial. JAMA 1995; 273: 934-41
20. Cohen J, Carlet J. INTERSEPT: an international, multicenter, placebo-controlled trial of monoclonal antibody to human tumor necrosis factor-alpha in patients with sepsis. Crit Care Med 1996; 24: 1431-40
21. Abraham E, NORASEPT II. The North American Sepsis Trial II: effect of murine monoclonal antibody (TNF Mab) in patients with septic shock [abstract no. 5067]. 20th International Congress of Chemotherapy: 1997 Jun 29-Jul 3; Sydney, 181
22. Fisher CJ Jr, Agosti JM, Opal SM, et al. Treatment of septic shock with the tumor necrosis factor receptor: Fc fusion protein. New Engl J Med 1996; 334: 1697-702
23. Abraham E, Glauser MP, Butler T, Ro 45-2081 Study Group, et al. p55 tumor necrosis factor receptor fusion protein in the treatment of patients with severe sepsis and septic shock: a randomized controlled multicenter trial. JAMA 1997; 277: 1531-8
24. Bone RC. Why sepsis trials fail. JAMA 1996; 276: 565-6
25. Abraham E, Raffin TA. Sepsis therapy trials: continued disappointment or reason for hope? JAMA 1994; 271: 1876-8
26. Zeni F, Freeman B, Natanson C. Anti-inflammatory therapies to treat sepsis and septic shock: a reassessment. JAMA 1997; 25: 1095-100
27. Bone RC, Sibbald WJ, Sprung CL, et al. ACCP/SCCM Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992; 101: 1644-55
28. Vincent JL. Dear SIRS, I'm sorry to say that I don't like you .. Crit Care Med 1997; 25: 372-74
29. Abraham E, Anzueto A, Gutierrez G, NORASEPT II Study Group, et al. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. Lancet 1998; 551: 929-33
30. Reinhart K for the RAMSES study group. Treatment of severe sepsis in patients with highly elevated IL-6 levels with anti-TNF monoclonal antibody-fragment afelimomab (MAK 195F): the RAMSES study. Poster presented at the 18th International Symposium of Intensive Care and Emergency Medicine. 1998 Mar 17-20; Brussels
31. Lynn WA, Golenbock DT. Lipopolysaccharide antagonists. Immunol Today 1992; 13: 271-6
32. Rustici A, Velucci M, Faggioni R, et al. Molecular mapping and detoxification of the lipid A binding site by synthetic peptides. Science 1993; 259: 361-5
33. Christ WJ, Asano O, Robidoux ALC, et al. E5531, a pure endotoxin antagonist of high potency. Science 1995; 268: 80-3
34. Munford RS, Hall CL. Detoxification of bacterial lipopolysaccharides (endotoxins) by a human neutrophil enzyme. Science 1986; 234: 203-5
35. Weiss J, Elsbach P, Olsson I, et al. Purification and characterization of a potent bactericidal and membrane active protein from the granules of human polymorphonuclear leukocytes. J Biol Chem 1978; 253: 2664-72
36. Hirata M, Shomomura Y, Yoshida M, et al. Characterization of a rabbit cationic protein (CAP18) with lipopolysaccharide-inhibitory activity. Infect Immun 1994; 62: 1421-6
37. Tanaka S, Nakamura T, Morita T, et al. Limulus anti-LPS factor: an anticoagulant which inhibits the endotoxin mediated activation of Limulus coagulation system. Biochem Biophys Res Commun 1982; 105: 717-23
38. Wurfel MM, Kunitake ST, Lichenstein H, et al. Lipopolysaccharide (LPS)-binding protein is carried on lipoproteins and acts as a cofactor in the neutralization of LPS. J Exp Med 1994; 180: 1025-35
39. Wurfel MM, Hailman E, Wright SD. Soluble CD14 acts as a shuttle in the neutralization of lipopolysaccharide (LPS) by LPS-binding protein and reconstituted high density lipoprotein. J Exp Med 1995; 181; 1743-5
40. Harris HW, Grunfeld C, Feingold KR, et al. Human very low density lipoproteins and chylomicrons can protect against endotoxin-induced death in mice. J Clin Invest 1990; 86: 696-702
41. Harris HW, Grunfeld C, Feingold KR, et al. Chylomicrons alter the fate of endotoxin, decreasing tumor necrosis factor release and preventing death. J Clin Invest 1993; 91: 1028-34
42. Levine DM, Parker TS, Donnelly TM, et al. *In vivo* protection against endotoxin by plasma high density lipoprotein. Proc Natl Acad Sci USA 1993; 90: 12040-4
43. Hubsch AP, Powell FS, Lerch PG, et al. A reconstituted apolipoprotein A-I containing lipoprotein reduces tumor necrosis factor release and attenuates shock in endotoxemic rabbits. Circ Shock 1993; 40: 14-23
44. Pajkrt D, Doran JE, Koster F, et al. Antiinflammatory effects of reconstituted high-density lipoprotein during human endotoxemia. J Exp Med 1996; 184: 1601-8
45. Pugin J, Heumann ID, Tomasz A, et al. CD14 is a pattern recognition receptor. Immunity 1994; 1: 509-16
46. Gallay P, Heumann D, Le Roy D, et al. Mode of action of anti-lipopolysaccharide-binding protein antibodies for prevention of endotoxemic shock in mice. Proc Natl Acad Sci USA 1994; 91: 7922-6
47. Ferrero E, Jiao D, Tsuberi BZ, et al. Transgenic mice expressing human CD14 are hypersensitive to lipopolysaccharide. Proc Natl Acad Sci U S A 1993; 90: 2380-4
48. Jack RS, Fan X, Bernheiden M, et al. Lipopolysaccharide-binding protein is required to combat a murine gram-negative bacterial infection. Nature 1997; 389: 742-5
49. Haziot A, Ferrero E, Kontgen F, et al. Resistance to endotoxin shock and reduced dissemination of Gram-negative bacteria in CD14-deficient mice. Immunity 1996; 4: 407-14
50. Paul A, Wilson S, Belham CM, et al. Stress-activated protein kinases: activation, regulation and function. Cell Signal 1997; 9: 403-10
51. Bernhagen J, Calandra T, Mitchell RA, et al. MIF is a pituitary-derived cytokine that potentiates lethal endotoxemia. Nature 1993; 365: 756-9
52. Calandra T, Bernhagen J, Mitchell RA, et al. The macrophage is an important and previously unrecognized source of macrophage migration inhibitory factor. J Exp Med 1994; 179: 1895-902
53. Calandra T, Bernhagen J, Metz CN, et al. MIF as a glucocorticoid-induced modulator of cytokine production. Nature 1995; 377: 68-71
54. Calandra T, Bucala R. Macrophage migration inhibitory factor (MIF): a glucocorticoid counter-regulator within the immune system. Crit Rev Immunol 1997; 17: 77-88
55. Docke W-D, Randow F, Styrhe U, et al. Monocyte deactivation in septic patients: restoration by IFN-γ treatment. Nature Med 1997; 3: 678-81
56. Volk HD, et al. Alterations in function and phenotype of monocytes from patients with septic disease: predictive value and new therapeutic strategies. In: Falst E, Meakins IL, editors. Host defense dysfunction in trauma, shock and sepsis. Berlin: Springer-Verlag, 1993

Correspondence and reprints: Dr *Jean-Daniel Baumgartner*, Service of Internal Medicine, Hôpital de Zone, CH-1110 Morges, Switzerland.