



POSITION STATEMENT

Severe sepsis and the role of novel therapeutic agents

Position statement of the Critical Care Society of South Africa on severe sepsis and the role of novel therapeutic agents such as drotrecogin alfa (activated)

Severe sepsis has an extremely high mortality rate of approximately 30 - 50%.¹ In addition, it appears that the incidence or the reporting of the condition is on the increase.^{2,3} Sepsis initiates the systemic inflammatory response syndrome with resultant capillary leak, disseminated intravascular coagulation (DIC), tissue ischaemia, and multiple organ dysfunction.^{4,5} The lung is the most common primary site of infection, followed by the abdomen and urinary tract.⁶ Determination of the site is not always easy and 20 - 30% of cases have no definite site or have negative cultures despite a high suspicion of sepsis.^{7,8}

Primary therapy should be prompt and should involve source control and appropriate antibiotic cover. Surgical eradication is the mainstay of therapy for focal sepsis.⁵ Antibiotics are not sufficient on their own; however, delay of adequate antibiotic therapy is associated with increased mortality.⁹ Empirical therapy may therefore have to be broad and may require de-escalation strategies to reduce the development of resistance to extended-spectrum agents.¹⁰

Lung failure and shock occur early and if inappropriately managed increase mortality.¹¹ Hypotension in cases of sepsis results primarily from a cytokine-mediated increase in endothelial nitric oxide and nitric oxide-mediated myocardial dysfunction. Therapy consists of fluid administration and appropriate inotropes, frequently guided by monitoring of cardiac output, systemic vascular resistance and stroke volume. Fluid should be administered as early as possible in a goal-directed manner. A recent study using a goal of central venous oxygen saturation of greater than 70% demonstrated significant outcome benefits (46.5% mortality v. 30.5% in the goal-directed group, $p = 0.009$).¹² Corticosteroids are frequently necessary and if used appropriately reduce length of stay and improve survival.^{13,14} Hydrocortisone should be used in patients with

refractory, catecholamine-dependent shock in a dose of 200 - 300 mg daily by infusion or in three divided doses. If initiated it should be continued for at least 7 days to prevent rebound in inflammation. It may be given with fludrocortisone.

Between 25% and 42% of patients with severe sepsis require ventilation.¹⁵ Ventilatory strategies impact on survival and have the potential to increase the inflammatory response.^{16,17} Pressures should be limited to less than 30 cm H₂O (plateau pressure with volume modes or peak pressure with pressure-control modes). Restriction of pressure is easiest to achieve with pressure controlled ventilation or BIPAP.

Tight glucose control reduces mortality, length of stay and complications associated with critical illness. This benefit is seen in the sickest patients and those who remain in the intensive care unit (ICU) the longest. Insulin is an anabolic hormone and infusion may have benefits other than merely the reduction of glucose levels.¹⁸ This requires the use of a well-defined protocol to avoid hypoglycaemia or intermittent hyperglycaemia. Although this study was performed in a surgical patient population, it is conceivable that this also applies to medical patients.

The unravelling of the pathogenesis of sepsis has led to the development of a promising new agent—activated protein C (APC), generic name drotrecogin alfa, trade name Xigris.¹⁹ This agent improved mortality in the PROWESS study by 6.1% (number needed to treat = 16) from 30.8% to 24.7% by reducing DIC and by modulating the inflammatory response.^{19,20} This benefit is seen particularly in those with an APACHE score of 25 or greater and in those with overt DIC, more elevated interleucin-6 and more organ dysfunction. The major complication is an increased bleeding rate, which is not unexpected as APC is an anticoagulant. The primary indications therefore would be any patient with severe sepsis as indicated by the presence of infection plus an APACHE score of ≥ 25 . It should be avoided where there is active bleeding, haemorrhagic stroke, recent central nervous system surgery, trauma and epidural catheterisation, and used with caution where there is a platelet count less than 30×10^9 , an international normalised ratio > 3 or severe chronic liver disease, in patients on dialysis, and in those who are immunocompromised or have recently undergone surgery. The agent should obviously be avoided in patients likely to die within a year from co-morbid disease, those at risk of recurrent

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sepsis, e.g. burns, and those not ill enough, i.e. an APACHE score less than 25. It costs in the region of R55 000 for a 4-day infusion. Its efficacy has not been established in children.¹⁹

The cost of this product in South Africa poses serious ethical dilemmas with regard to the allocation of scarce and expensive resources. Available cost-effectiveness data are not directly applicable in the South African context.²¹ Differences in economies of scale in developed and developing countries make direct extrapolation of such data difficult. The dichotomous nature of health care provision in our country has produced gross disparities in available funding in the private and public health care systems. Cost-containment imperatives in both sectors will undoubtedly impact on affordability of novel, expensive therapies. Significant advances have been made in a number of areas with regard to the management of sepsis. However, administration of this prohibitively expensive drug without attention to basic supportive measures would negate the positive effects seen in the PROWESS study.¹⁹ As a consequence we believe that this agent should only be prescribed by intensivists and that a checklist should be utilised (available from the Critical Care Society) to assess whether all other appropriate therapeutic measures have been effectively implemented. In the private sector a call centre driven by intensivists is recommended to ensure appropriate utilisation of this expensive resource. The Critical Care Society is willing to support the development of this facility. In the public sector, where many ICUs function as closed units and are run or supported by intensivists, it is likely that this drug may never be prescribed as a consequence of its cost. The Critical Care Society supports the concept of differential drug pricing as is the case for antiretroviral therapy in South Africa. The manufacturer is therefore urged to consider adopting this

approach to ensure greater availability of this drug to all South Africans.

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