

# Septic shock: the changing Zeitgeist of management

Allen C Cheng<sup>1\*</sup> and Dianne P Stephens<sup>2</sup>

Address: <sup>1</sup>Division of Medicine, Royal Darwin Hospital and Menzies School of Health Research, Charles Darwin University, PO Box 41096, Casuarina, NT 0811, Australia; <sup>2</sup>Intensive Care Unit, Royal Darwin Hospital, Rocklands Drive, Tiwi, NT 0810, Australia

\*Corresponding author: Allen C Cheng (allen.cheng@menzies.edu.au)

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## Abstract

Most interventions in critically unwell patients with septic shock are poorly supported by evidence, in part reflecting the difficulty of conducting trials in this heterogeneous group. Four important clinical trials in 2001-2 appeared to demonstrate mortality benefits associated with early goal-directed resuscitation, intensive glycaemic control, physiological-dose steroid replacement and activated protein C. However, recent evidence has not confirmed the beneficial effect of these interventions.

## Introduction and context

Early in 2008, the Surviving Sepsis Campaign updated guidelines for the management of septic shock [1]. Although endorsed by a large number of international organizations (but notably not the Australian and New Zealand Intensive Care Society [2]), previous guidelines had been controversial for their support by the pharmaceutical industry, and for some of the previous recommendations advocating interventions that were not well supported by the evidence [3]. Whatever the criticisms of the specific recommendations, evidence does suggest that educational programs based on implementing the guidelines are associated with improved outcomes in observational studies [4,5].

Four landmark studies published in 2001 and 2002 appeared to show improvements in mortality associated with certain therapeutic strategies: the use of physiological-dose steroid replacement [6]; the strict maintenance of blood sugar by insulin infusions [7]; the use of early goal-directed fluid resuscitation [8]; and the use of activated protein C (drotrecogin alfa) [9]. The updated guidelines take a more balanced approach to recommendations, particularly in the light of recent published trials (Table 1). Unfortunately, these studies appear to have joined the shortlist of promising strategies that have been tempered by practical considerations and later studies [10].

## Recent advances

### *Steroid replacement revisited*

In 2002, a multicentre trial of physiological-dose steroid replacement against placebo in patients with septic shock was published which suggested that the use of hydrocortisone and fludrocortisone at 'stress replacement' doses was associated with a reduction in mortality in the subgroup of patients that had 'relative adrenal insufficiency' [6]. The effect on surrogate endpoints, such as the duration of shock and duration of survival, appeared to be consistent with the effect of steroid replacement.

However, several concerns were raised, resulting in doubts regarding the generalizability of this study. First, the primary endpoint in all patients was not statistically different at 28 days, with the benefit seen primarily in the subgroup defined by a poor response to stimulation with adrenocorticotrophic hormone (ACTH). The overall mortality and the proportion of patients with relative adrenal insufficiency seemed high; the use of etomidate, a known inhibitor of adrenal function, may have contributed to the latter [11,12]. In this study [6], all assays were performed at a central laboratory, and studies have demonstrated significant heterogeneity between different cortisol assays [13].

The CORTICUS study has recently been published, examining the effect on mortality of hydrocortisone on

**Table 1. Selected randomized controlled trials in severe sepsis and septic shock**

Study	Patient group	Intervention/comparator	Outcomes	Comments
<b>Physiological-dose steroids</b>				
Annane, 2001 [5]	Septic shock (n = 300)	Hydrocortisone (50 mg iv q 6 h) and fludrocortisone (0.1 mg po daily) for 7 days vs placebo	28-day mortality: 5 vs 61% (P = 0.09)	Benefit seen in ACTH non-responders (63 vs 53%, P = 0.04). Included patients on etomidate (n = 77) prior to change in protocol
CORTICUS, 2008 [14]	Septic shock (n = 499)	Hydrocortisone (50 mg iv q 6 h) for 5 days vs placebo	28-day mortality: 3 vs 32% (P = 0.51)	Patients on etomidate (n = 96) not excluded. No benefit in ACTH non-responders (39 vs 36%). Increased incidence of superinfection in steroid group (33 vs 26%)
<b>Intensive glycaemic control</b>				
Van den Berghe, 2001 [7]	Surgical ICU patients requiring mechanical ventilation (n = 1548)	Insulin infusion to achieve target glucose 4.4-6.1 mmol/l vs target glucose 10.0-11.1 mmol/l	In-hospital mortality: 7.2 vs 10.9% (P = 0.01)	Benefit seen in patients requiring >5 days intensive care (26 vs 17%). Difference in death due to incident severe sepsis. Increased proportion with hypoglycaemia (5.1 vs 0.8%)
Van Den Berghe, 2006 [15]	Medical ICU patients (n = 1200)	Insulin infusion to achieve target glucose 4.4-6.1 mmol/l vs target glucose 10.0-11.1 mmol/l	In-hospital mortality: 37.3 vs 40.0% (P = 0.33)	Higher rates of hypoglycaemia (18.7 vs 3.1%, P < 0.001)
WISEP, 2008 [16]	Severe sepsis or septic shock (n = 537)	Insulin infusion to achieve target glucose 4.4-6.1 mmol/l vs target glucose 10.0-11.1 mmol/l	28-day mortality: 24.7 vs 26.0% (P = 0.74)	Factorial trial with pentastarch. Higher proportion of patients with hypoglycaemia (17 vs 4.1%, P < 0.001)
<b>Early goal-directed resuscitation</b>				
Rivers, 2001 [8]	Patients presenting to ED with severe sepsis or septic shock (n = 263)	Therapy guided by SvO <sub>2</sub> monitoring vs standard resuscitation (see text)	In-hospital mortality: 30.5 vs 46.5% (P = 0.009)	Single-centre study, patient management in emergency department
<b>Drotrecogin alfa</b>				
PROWESS, 2001 [9]	Severe sepsis (n = 1690)	Drotrecogin alfa (24 µg/kg/h) for 96 h vs placebo	28-day mortality 24.7 vs 30.8% (P = 0.005)	Mortality benefit seen in high-risk patients only (in subgroup analysis). Increase in serious bleeding (3.5 vs 2%)
ADDRESS, 2005 [20]	Severe sepsis but low risk of death (either APACHE II score < 25 or single organ failure) (n = 2640)	Drotrecogin alfa (24 µg/kg/h) for 96 h vs placebo	28-day mortality: 18.5 vs 17%, (P = 0.34)	Increase in serious bleeding (2.4 vs 1.2%, P = 0.02)
RESOLVE, 2007 [21]	Children < 18 years with septic shock (n = 477)	Drotrecogin alfa (24 µg/kg/h) for 96 h vs placebo	28-day mortality 17.2 vs 17.5%, (P = 0.93)	No difference in time to resolution of organ dysfunction

its own [14]. In this study, a significant proportion of patients received etomidate (19%), a high proportion had relative adrenal insufficiency (51%) and overall mortality was lower than in the previous study [6]. The use of physiological-dose hydrocortisone was not associated with a reduction in mortality (mortality benefit). Although the duration of shock was shorter in patients receiving hydrocortisone, the incidence of recurrent septic shock was also higher. The Surviving Sepsis Guidelines have been updated to reflect this, with hydrocortisone now only recommended for patients not responding to fluids and vasopressors, and the ACTH stimulation test no longer routinely recommended [1].

#### **Insulin infusions revisited**

In 2001, Van den Berghe and colleagues [7] published a clinical trial in which surgical patients in intensive care were randomized to receive either intensive glycaemic control using an insulin infusion, or standard treatment.

The target blood sugar in the intervention group was 4.4 to 6.1 mmol/l and was achieved by use of an insulin infusion. Intensive glycaemic control was associated with a 3.4% reduction in mortality, with benefits confined to the subgroup of patients that had a length of stay exceeding five days.

However, concerns focused on the poor glycaemic control in the comparator arm, in which blood glucose was maintained between 10 and 11.1 mmol/l; in addition, patients were given an unusual feeding protocol. Other investigators also had difficulties in implementing the protocol without a significant rate of hypoglycaemia. Furthermore, the group studied included only post-surgical patients with a low level of mortality, and uncertainty remained over the benefit of glycaemic control in medical patients.

Later studies have not confirmed the benefits of intensive glycaemic control in medical patients. In a follow-up study, intensive glycaemic control was not associated with a mortality benefit in a medical intensive care unit, and although a benefit was seen in a subgroup of patients with a length of stay exceeding three days, this group could not be identified prospectively [15]. Intensive glycaemic control was not associated with a mortality benefit in another clinical trial in interdisciplinary intensive care units that was stopped early because of the high incidence of hypoglycaemia [16].

Faced with the uncertainty regarding the risks and benefits of intensive glycaemic control, the Surviving Sepsis Guidelines now recommend a more modest blood glucose target of less than 8.3 mmol/l, despite the lack of supporting evidence for this target [1]. A large clinical trial, NICE-SUGAR, has been initiated in Australia and Canada and will hopefully define the appropriate glucose targets and patient group [2].

#### **Early goal-directed resuscitation revisited**

Aggressive early resuscitation is supported by the early goal-directed therapy (EGDT) protocol, which attempts to optimize several haemodynamic parameters within the first 6 hours in the emergency department. Resuscitation measures include the administration of fluids, pressor and inotropic agents and red cell transfusion. The intervention goals included central mixed venous oxygen saturation (SvO<sub>2</sub>) that was measured with a specialized central venous catheter. Use of a protocol targeted at achieving an SvO<sub>2</sub> of greater than 70%, in addition to the goals set in the control group, was associated with a mortality benefit when compared with a single-centre study of a protocol guided by central venous pressure and routine haemodynamic markers only [8].

Some have argued that it is the timing of the intervention that is associated with benefit rather than the use of specific outcome measures. This is supported by a meta-analysis of studies that showed that early intervention was associated with a mortality benefit, but later intervention was not [17]. Analogously, the administration of antibiotics early was also associated with reduced mortality in an observational study [18].

Several clinical trials have been initiated to try to confirm the observed benefit of the EGDT protocol, which has not been widely adopted in its original form. As an indicator of the uncertainty associated with this intervention, clinicians are readily participating in two large clinical trials that have recently been initiated to resolve the question.

#### **Activated protein C revisited**

Many unsuccessful attempts have been made in the past to modulate the immune response in severe sepsis. In 2001, the PROWESS study suggested that a significant benefit was seen in a placebo-controlled trial of drotrecogin alfa [9]. In this study, there was a 6.1% reduction in 28-day mortality. However, the very high cost of the drug, the question of whether the benefit was restricted to a particular patient group, and controversies around the approval process and marketing of the drug led to poor uptake of this therapy [3,19]. A subsequent subgroup analysis appeared to demonstrate benefit only in patients at high risk of death, and later trials in less severely unwell adult patients [20], and in children [21] have been negative. The clinical uncertainty surrounding the efficacy of drotrecogin alfa has led to calls for a repeat trial to confirm the findings of the PROWESS trial [22], and a clinical trial was initiated in late 2006.

#### **Implications for clinical practice**

##### **Sepsis bundles**

Although not explicitly spelled out in the guidelines, the general message from recent studies is that protocol-driven management that addresses the organ dysfunction associated with severe sepsis early on appears to be associated with improved outcomes. Such protocols have been termed 'sepsis bundles'. It is unclear which component of the EGDT is associated with improvements in mortality; for example, in a large Spanish study, mortality fell after implementation of an educational campaign based on the 'sepsis bundles', despite the post-intervention cohort patients achieving benchmark goals for central venous pressure and central venous oxygen saturation in only 27% and 11% of cases, respectively, with no significant difference in the time taken to achieve them [5]. Similarly, the proportion of patients in which drotrecogin alfa was considered for use rose from 44 to 52%, but it was only actually used in 56%: it is difficult to see how merely considering to use a medication might have an impact on mortality.

Mortality benefits in severe sepsis appear to be more linked to the early and systematic measurement and management of organ dysfunction, and are less dependent on the choice of the precise measure and specific intervention. The appropriate blood glucose target, the use of cardiac output monitoring, central venous oximetry and the choice of inotropes will continue to be debated. Recent trials have failed to confirm the promise of low-dose steroid replacement and intensive glycaemic control, and considerable uncertainty remains regarding the efficacy of drotrecogin alfa. Ongoing efforts

at early intervention and attention to detail is likely to continue to be the most effective management strategy.

## Abbreviations

ACTH, adrenocorticotrophic hormone; ED, emergency department; EGDT, early goal-directed therapy; ICU, intensive care unit; iv, intravenous; q, quarterly; SvO<sub>2</sub>, central mixed venous oxygen saturation.

## Competing interests

The authors declare that they have no competing interests.

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