

REVIEW

Early goal-directed therapy: a UK perspective

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The surviving sepsis campaign developed guidelines in 2003 that were designed to increase physician awareness of sepsis and to develop a series of recommendations for the management of the patient with sepsis. The guidelines had the support of 11 international professional organisations across a variety of specialties, and advocate aggressive, early goal-oriented resuscitation in appropriate patients.

of haemodynamic optimisation in critically ill patients initiated before the development of organ failure carried a marked mortality benefit compared with those that looked at optimisation after organ failure was established.

Rivers *et al*¹ published their work on EGDT in severe sepsis and septic shock in 2001. The effect of their work is potentially profound for emergency physicians, because it advocates a formula for aggressive resuscitation based primarily in the emergency department. Their randomised controlled trial compared a protocol for EGDT (fig 1), with standard therapy for 263 patients presenting to the emergency department with a diagnosis of severe sepsis or septic shock over a 3-year period. All patients recruited had both central and arterial lines placed, with those assigned to goal-directed therapy having a central line placed capable of continuous central venous oxygen saturation monitoring (ScvO₂). In addition to standard therapy these patients received

In 2001, Rivers *et al*¹ published a landmark study showing that an aggressive, goal-oriented resuscitation protocol administered in the emergency department reduced mortality from septic shock by 16%. The study showed that early, rapid, and decisive intervention saves lives. This is an intervention far more efficacious than thrombolysis for either acute myocardial infarction or thromboembolic stroke. The study also challenges us to examine how evidence of improved outcomes can be translated into bedside practice. In this case the key change in practice is a positive move towards earlier recognition and identification of patients with sepsis and the acknowledgement that global tissue hypoxia resulting from poor perfusion is one of the major physiological processes that we must deal with. There are many emergency departments across the US that have successfully implemented goal-directed therapy, a practice strongly backed by the surviving sepsis campaign.² Despite the increasing body of evidence pointing towards a more aggressive approach to the recognition and management of patients with sepsis, and evidence that early goal-directed therapy (EGDT) is feasible in the emergency department setting,^{3–5} there seems to be a general reluctance to adopt this approach within emergency departments in the UK.⁶

We review the origins of goal-directed therapy, potential obstacles to its implementation and describe the effect and opportunity for the UK health system.

Where does goal-directed therapy come from?

The modern day upsurge in interest in goal-directed therapy was probably ignited by Shoemaker *et al*⁷ in 1988 with their work on the use of supranormal oxygen levels in post-operative patients. Subsequent work by Boyd *et al*⁸ and Gattinoni *et al*⁹ gave support both for and against the developing concept of goal-oriented therapy. The approach of Rivers¹ reflected the results of a meta-analysis by Kern and Shoemaker.¹⁰ This had shown that those studies

- aggressive fluid resuscitation (500 ml boluses of crystalloid or colloid to maintain central venous pressure (CVP) \geq 8 mm Hg)
- vasopressors or dilators to maintain mean arterial pressure (MAP) between 65 and 90 mm Hg
- red blood cell transfusions to attain a haematocrit \geq 30% in patients with ScvO₂ of <70%
- inotrope infusions for patients with low ScvO₂ despite a normalised haematocrit.

The key difference between the treatment and control groups was the attempted optimisation of ScvO₂, with those patients whose targets could not be met being electively intubated and mechanically ventilated. The authors showed a 16.5% reduction in in-hospital mortality for patients in their treatment group (30% v 46.5%; $p = 0.009$), with a relative risk reduction of 32.3% (28-day mortality) and a number needed to treat of six.

Subsequent studies have shown that EGDT is feasible in the emergency department.^{3–5} Mortality from sepsis remains high despite advances in the management of patients in intensive care units, at around 30%.¹⁰ Conditions with a higher profile such as myocardial infarction have remained treatment priorities, despite lower in-hospital mortality (10%) and the relatively poor benefit from thrombolysis (number needed to treat >20).

Abbreviations: CVP, central venous pressure; EGDT, early goal-directed therapy; MAP, mean arterial pressure; ScvO₂, central venous oxygen saturation; SvO₂, venous oxygen saturations.

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showed the importance of microvascular flow by studying 49 patients with septic shock, where although haemodynamic and oxygenation profiles were initially similar, non-survivors had substantially reduced microcirculatory changes and small-vessel perfusion.

What are the components of goal-directed therapy?

Fluid resuscitation and CVP monitoring

It is well-recognised that patients with septic shock are likely to be fluid depleted¹⁶ and that these fluid losses may be either absolute (for example due to diarrhoea, sweating or oedema) or relative (with fluid redistributed and pooled in the dilated peripheral vasculature). The potential effects of this hypovolaemia are central to the changes that are subsequently seen in patients who have severe sepsis and septic shock, with poor perfusion and compromise of the microcirculation.¹³ The debate about the relative merits of different fluids for resuscitation in general has been fierce, but there is little evidence to strongly advocate the preferential use of either crystalloids or colloids in sepsis with or without shock or organ dysfunction.¹⁶ Fluid resuscitation alone can help to reduce the global tissue hypoxia that is central to the development of multiorgan dysfunction, by increasing the cardiac output and improving oxygen delivery to the tissues.¹⁷

The ultimate key to satisfactory fluid resuscitation is a regular reassessment of appropriate end points of resuscitation and response to therapy. These may be physiological parameters (pulse rate, MAP and CVP), biochemical parameters (serial lactate measurements), clinical parameters (peripheral perfusion, urine output and pulmonary oedema) or perhaps, ideally, a combination of all of these.

MAP and vasopressors

Hypotension and impaired end-organ perfusion are recognised features of septic shock. Even after adequate fluid resuscitation many patients remain hypotensive or have inadequate tissue perfusion as a result of microvascular changes, myocardial depression, vasodilatation and maldistribution of cardiac output.¹⁸ Patients who remain hypotensive after adequate fluid resuscitation are started on vasopressors in an attempt to restore organ perfusion and improve oxygen delivery. The protocol for EGDT advocates using **vasoactive agents (either vasopressors or intravenous nitrates) to target the MAP between 65 and 90 mm Hg**. Most patients will require vasopressors rather than nitrates. In the **Rivers study**,¹ patients received norepinephrine, epinephrine, dopamine or phenylephrine hydrochloride. In practice, the vasopressor that a particular patient requires will depend on their specific clinical condition and also the views of the treating clinician.

The use of arterial catheters for invasive blood pressure monitoring is essential to guide the resuscitation of patients with sepsis.¹⁹ Conventional non-invasive blood pressure monitoring may be inaccurate and does not allow the beat-to-beat analysis that invasive monitoring provides. In addition, in patients who will need repeated arterial blood gas analysis, it would seem preferable to reduce the need for multiple needlesticks.

ScvO₂ monitoring and blood transfusion

The use of ScvO₂ as a surrogate for measuring the balance between oxygen supply and delivery to the tissues is also controversial. Certainly, mixed venous oxygen saturations have been shown to be a useful marker for cardiac index as a target for resuscitation. Increasing the oxygen delivery to critically ill patients has been shown to result in an increase in the ScvO₂.¹⁹

Intensivists may argue that ScvO₂ does not accurately reflect the **mixed venous oxygen saturations (SvO₂)** and that pulmonary artery catheterisation is preferable to obtain an

accurate value. In patients in the intensive care setting in whom a pulmonary artery catheter is indicated, then, SvO₂ measurement may be preferable. Reinhart *et al*²⁰ have suggested that there is evidence to support an SvO₂ of 65% being roughly equivalent to an ScvO₂ of 70%, recognising that although there is some difference in the absolute value, the ScvO₂ may be used as a good approximation. Ladakis *et al*²¹ compared the ScvO₂ and SvO₂ in 61 mechanically ventilated ITU patients and found the values to be very closely related and even interchangeable for the initial management of critically ill patients.

Rivers used a central line capable of giving ScvO₂ monitoring, but it is unclear whether this is essential for adequate monitoring.¹ It may be possible to achieve an adequate level of monitoring using intermittent sampling from the central line and feeding samples through a blood gas analyser.

The use of blood transfusions in patients with sepsis remains controversial.²³ The potential benefit is of increased delivery of oxygen to tissues that are hypoxic with the aim of reducing the degree of ongoing ischaemia.²⁴ The risks and complications of transfusion are well-recognised and include transmission of microorganisms; transfusion-related immunomodulation, which may increase the risk of infections; transfusion-related acute lung injury; and human errors.²⁵ However, there is little evidence that this increased oxygen delivery is matched by an increase in oxygen consumption by the tissues in sepsis, and there might be other more complex factors that lead to the improvement in tissue oxygenation.¹⁸ The haemoglobin level required for optimum function in patients with sepsis is unknown. The Transfusion Requirements in Critical Care Study suggests a haemoglobin level of **7–9 g/dl as being adequate** for patients with sepsis, but it is known that certain patients will benefit from having a higher haemoglobin level, such as those with known cardiovascular disease or those with evidence of organ or tissue ischaemia.^{24 25} Patients in the second group may be recognised as having mixed venous oxygen desaturation or an increased lactate level, and it is these patients who are targeted by goal-directed therapy. EGDT differs in principle from the Transfusion Requirements in Critical Care Study. The Transfusion Requirements in Critical Care Study treatment group was associated with indiscriminate transfusion to a baseline hematocrit, whereas EGDT reflects a strategy using targeted end points to **manipulate the oxygen delivery equation** to increase oxygen supply in those with a measured oxygen deficit.

Who should receive EGDT?

Early recognition is one of the key facets of EGDT, yet recognition of patients with sepsis may not always be as straightforward as one might expect.²⁶ Patients presenting with fever, tachycardia and hypotension and an obvious septic focus do not provide a great diagnostic challenge but many will present without these signs. The average temperature of patients in the Rivers paper in both treatment and control groups was <37°C.¹ This would suggest that to rely on temperature alone as a key diagnostic criterion would lead to the exclusion of a large number of potentially eligible patients.

Patients with septic shock will by definition be hypotensive and may have other evidence of impaired perfusion, such as increased capillary refill time, confusion and reduced urine output. It is the patients who are at a much earlier point in the sepsis continuum who may be far more difficult to identify, yet in whom an early aggressive approach to resuscitation may be most beneficial. Donnino *et al*²⁷ carried out a retrospective analysis of EGDT patients presenting to the emergency department showing that patients with severe

sepsis and lactic acidosis may have global tissue hypoxia despite the absence of hypotension. Aggressive treatment of this group of patients with EGDT conferred a significant mortality benefit (20% v 60.9%; $p < 0.004$).

Although an increased serum lactate level does not define sepsis, Rivers used it as one of the entry criteria for patients to receive goal-directed therapy in conjunction with the systemic inflammatory response syndrome criteria. Poor tissue perfusion and reduced oxygen delivery (DO_2) result in anaerobic metabolism, with the production of lactic acid. Thus, serum lactate levels may be used to reflect the level of tissue hypoperfusion. Some studies have suggested that the increase in serum lactate levels may actually reflect a failure of cellular metabolism rather than hypoperfusion and anaerobic metabolism,²⁸ but either way it has a role as a prognostic indicator.¹⁶ Shapiro *et al*²⁶ looked at serum lactate levels as a predictor of mortality in patients in the emergency department with a diagnosis of sepsis, showing that a serum lactate level of >4 mmol/l was associated with a mortality of 28%.

What is the UK perspective?

Much of the work to date looking at the use of EGDT in the management of patients with sepsis has been undertaken in the US. There seems little doubt that with more than 751 000 cases of severe sepsis per year in the US and a mortality of between 30% and 50%, this represents a major problem in their population.²⁶ The statistics suggest that although there has been a steady increase in the incidence of the various sepsis syndromes, there has been little change in the mortality over time, certainly until the introduction of EGDT.²⁹ UK data from the Intensive Care National Audit and Research Centre database would suggest that with mortality approaching 50% and more than 10 000 deaths in 2001, sepsis also represents a major problem in this country and one that is worthy of attention.

A recent study from a teaching hospital in Melbourne has questioned the incidence of sepsis and septic shock among patients in the emergency department and hence the value of implementing programmes as rigorous as EGDT. They reported that only 1.6% (78 patients) of their 4700 attendances to the emergency department afforded a diagnosis of infection over a 3-year period fulfilled the entry criteria for EGDT.³⁰ However, even in the absence of a protocol for goal-oriented therapy, $>70\%$ of the eligible patients had invasive monitoring with arterial and central lines, had started vasopressor therapy in the emergency department and received antibiotics within 6 h of arrival. This probably represents an underestimate of the scale of the problem, without the inclusion of patients who were either managed exclusively on the general wards or those who were managed initially on the general wards, but subsequently required admission to the intensive care unit. Together, these represent a significant group of patients, including those who may stand to receive greatest benefit from EGDT before the onset of organ failure. In addition, the authors used a base excess of -3 mEq/l or worse as a surrogate for raised lactate levels in identifying eligible patients, excluding a small but important group of patients with raised lactate levels, but a base excess within the normal range.

Two of the authors (AR and AA) carried out a retrospective activity analysis of early resuscitation of patients presenting with severe sepsis and septic shock at Derriford hospital, a major teaching hospital in Plymouth, UK. All adult patients presenting through the emergency department over a 12-month period with severe sepsis and septic shock were included. Patients were identified through three main sources. The emergency department patient database, which includes all patients attending the emergency department,

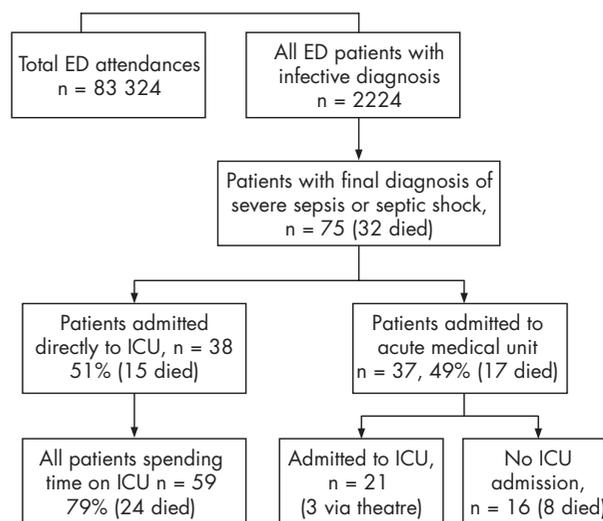


Figure 2 Outcomes of patients presenting to the emergency department (ED) with severe sepsis or septic shock. ICU, intensive care unit

Table 1 Baseline characteristics of patients during audit period compared with early goal-directed therapy

	Authors' sepsis audit	Rivers EGDT (control)
No of patients (period)	75 (1 year)	130 (3 years) (133)
Mean age	61.8	67.4 (67.1)
Mean APACHE II	18.3	16.0 (17.6)
In-hospital mortality (%)	42.6	30.5 (46.5)

APACHE II, Acute Physiology And Chronic Health Evaluation; EGDT, early goal-directed therapy.

was interrogated for patients coded to cover all possible infectious diagnoses at any site. This provided most of the cases. In addition, the Intensive Care National Audit and Research Centre database was reviewed for all patients with severe sepsis or septic shock, admitted either directly from the emergency department or via the acute medical unit from patients presenting initially to the emergency department. Finally, the stored database of the blood gas analyser was reviewed to identify all patients with a serum lactate level of ≥ 4 , and this was cross-referenced to the other two groups to identify any eligible patients who may have been missed. Of a total of 83 324 emergency department attendances, 2224 had an infective diagnosis attributed to them and of these 75 patients had a final diagnosis of severe sepsis or septic shock (fig 2), 32 (43%) of whom died. Of the 75 patients, 38 (51%) were admitted to the intensive care unit, and the remaining 37 (49%) directly to the acute medical ward. Twenty one of the 37 patients who went to the medical ward (57%) subsequently deteriorated and were transferred to the intensive care unit. Of the 16 patients who remained on the acute medical ward, 8 survived to discharge and 8 died. Of the 59 patients who spent some time on the intensive care unit, 24 (32%) died. Table 1 shows how the baseline characteristics of patients compared with those in the EGDT trial; and table 2 shows the difference between the patients in terms of monitoring and therapy. Although the percentage of patients receiving antibiotics in the emergency department was comparable, there were clear differences between the volume of fluid resuscitation, number of patients with invasive monitoring, use of vasopressors and packed red cell transfusion.

Table 2 Resuscitation during first 6 h of audit period compared with early goal-directed therapy

First 6 h of care	Authors' sepsis audit (n = 59)	Rivers EGDT (n = 130)
Antibiotics given in the ED (%)	70	86
Mean fluid resus in ml (SD)	2970 (1918)	4981 (2438)
CVP monitoring in ED (%)	22.5	100
Vasopressor in ED (%)	7.4	27.4
Red cell transfusion (%)	0	64.1
Time in ED (mean)	4:50	8:00

CVP, central venous pressure; ED, emergency department; EGDT, early goal-directed therapy; resus, resuscitation.

What does the future hold?

Rivers himself pointed out that EGDT was not an emergency department study, but a study that provided best care to the patients with sepsis as early as possible.¹¹ The question remains of whether the protocol he described is appropriate for implementation in this country. There is now good evidence to support the beneficial effects shown by Rivers.¹¹ More recently, Shapiro *et al*⁴ and Trzeciak *et al*⁵ have shown that EGDT end points can reliably be achieved in clinical practice without the use of dedicated study teams. The available evidence suggests that this is a problem worthy of our attention and that an early aggressive approach can confer marked mortality benefit in a group of patients who are traditionally underdiagnosed and undertreated. As a body in emergency medicine in the UK, we have taken the lead for the thrombolysis of patients with acute myocardial infarction—a group of patients with an 8% risk of death in the first 30 days, using a therapy that provides an absolute risk reduction of 5% and an number needed to treat of >20. We are now moving towards a more aggressive approach to those having had thromboembolic strokes—12 to 19% risk of death in the first 30 days, and an as yet unknown absolute risk reduction. Yet, we seem reluctant to break down some traditional barriers and beliefs and strike up an effective collaboration with critical care. This would enable us to manage more appropriately a group of patients with a mortality of >30%, using a therapy shown to confer an absolute risk reduction of 16%,¹ with a number needed to treat of 6, and which has been shown to be practically feasible.

CONCLUSIONS

EGDT has been shown to improve survival for patients in the emergency department with severe sepsis and septic shock¹ and has been advocated by the surviving sepsis campaign,² itself supported by 11 international organisations. Local audit has shown that a UK population has characteristics similar to those of the original study group, in terms of the emergency department incidence of septic shock. This is a standard of care that we should now be implementing in our departments.

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REFERENCES

- Rivers E, Nguyen B, Havstad S, *et al*. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;**345**:1368–77.
- Dellinger RP, Carlet JM, Masur H, *et al*. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;**32**:858–73.
- Nguyen HB, Corbett SW, Menes K, *et al*. Early goal-directed therapy, corticosteroid and recombinant activated protein C for the treatment of severe sepsis and septic shock in the emergency department. *Acad Emerg Med* 2006;**13**:109–113.
- Shapiro NI, Howell MD, Talmor D, *et al*. Implementation and outcomes of the multiple urgent sepsis therapies (MUST) protocol. *Crit Care Med* 2006;**34**:1025–32.
- Trzeciak S, Dellinger RP, Abate NL, *et al*. Translating research to clinical practice: a 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. *Chest* 2006;**129**:225–33.
- Jones AE, Kline JA. Use of goal-directed therapy for severe sepsis and septic shock in academic emergency departments. *Crit Care Med* 2005;**33**:1888–9.
- Shoemaker WC, Appel PL, Kram HB, *et al*. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988;**94**:1176–86.
- Boyd O, Grounds RM, Bennett, eds. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high risk surgical patients. *JAMA* 1993;**270**:2699–707.
- Gattinoni L, Brazzi L, Pelosi P, *et al*. A trial of goal-orientated hemodynamic therapy in critically ill patients. *N Engl J Med* 1995;**333**:1025–32.
- Kern JW, Shoemaker WC. A meta-analysis of hemodynamic optimization in high risk patients. *Crit Care Med* 2002;**30**:1686–92.
- Rivers EP. Early goal-directed therapy in severe sepsis and septic shock: converting science to reality. *Chest* 2006;**129**:217–8.
- Hayes MA, Timmins AC, Yau EHS, *et al*. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994;**330**:1717–22.
- Bateman RM, Walley KR. Microvascular resuscitation as a therapeutic goal in severe sepsis. *Crit Care* 2005;**9**(Suppl 4):S27–32.
- Ensinger H, Georgieff M. Is infection and septic shock caused by a global oxygen deficiency? An overview in 2 parts. 1: infection and correlation between DO₂ and VO₂. *Anesthesiol Intensivmed Notfallmed Schmerzther* 1996;**31**:132–142.
- Sakr Y, Dubois MJ, De Backer D, *et al*. Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Crit Care Med* 2004;**32**:1825–31.
- Vincent J-L, Gerlach H. Fluid resuscitation in severe sepsis and septic shock: an evidence based review. *Crit Care Med* 2004;**32**(Suppl):11.
- Haupt MT, Gilbert EM, Carlson RW. Fluid loading increases oxygen consumption in septic patients with lactic acidosis. *Am Rev Respir Dis* 1985;**131**:912–16.
- Beale RJ, Hollenberg SM, Vincent J-L, *et al*. Vasopressor and inotropic support in septic shock: an evidence-based review. *Crit Care Med* 2004;**32**(Suppl):S455–65.
- Yu MY, Burchel S, Hasaniya N, *et al*. Relationship of mortality to increasing oxygen delivery in patients > or = to 50 years of age: a prospective, randomized trial. *Crit Care Med* 1998;**26**:1011–19.
- Reinhart K, Kuhn HJ, Hartog C, *et al*. Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. *Int Care Med* 2004;**30**:1572–8.
- Ladakis C, Myrianthefs P, Karabinas A, *et al*. Central venous and mixed venous oxygen saturation in critically ill patients. *Respiration* 2001;**68**:279–85.
- Vincent J-L, Baron J-F, Reinhart K, *et al*. Anemia and blood transfusion in critically ill patients. *JAMA* 2002;**288**:1499–1507.
- Zimmerman JL. Use of blood products in sepsis: an evidence-based review. *Crit Care Med* 2004;**32**(Suppl):S542–7.
- Vincent J-L, Piagnerelli M. Transfusion in the intensive care unit. *Crit Care Med* 2006;**34**:S96–101.
- Hebert PC, Wells G, Blajchman MA, *et al*. A multicentre randomised controlled clinical trial of transfusion in critical care. *N Engl J Med* 1999;**340**:409–17.
- Shapiro NI, Howell MD, Talmor D, *et al*. Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med* 2005;**45**:524–8.
- Donnino MW, Nguyen B, Jacobsen J, *et al*. Cryptic septic shock: a sub-analysis of early goal-directed therapy. *Chest* 2003;**124**:905.
- Vincent J-L, Dufaye P, Berre J. Serial lactate determinations during circulatory shock. *Crit Care Med* 1983;**11**:449–51.
- Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed with time? *Crit Care Med* 1998;**26**:2078–86.
- Ho BC, Bellomo R, McGain F, *et al*. The incidence and outcome of septic shock patients in the absence of early-goal directed therapy. *Crit Care* 2006;**10**:R80.



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