Controversies in Early Goal Directed Therapy in Sepsis

Severe sepsis and septic shock is one of the commonest diagnosis in the critically ill and, despite advances in our understanding of its pathophysiology as well as newer antibiotics, these clinical conditions still have poor prognosis. Sepsis and septic shock lead to multiple organ dysfunction syndrome (MODS) which is the leading cause of death in this condition. It is thus highly desirable to have management principles in place that can treat sepsis/septic shock and reduce morbidity and mortality. Early Goal Directed Therapy (EGDT) in sepsis is one such management protocol that has gained popularity over the last decade or so.

Some historical background:

Time honoured initial clinical management of the critically has involved initiation of oxygen therapy, administration of fluids and sooner or later pharmacological support of cardiovascular system (inotropes, vasoactive drugs). This line of initial management has been based on observations that critically ill patients are almost always (but not invariably) hypovolaemic and exhibit signs of organ hypoperfusion with or without actual hypotension; this hypoperfusion leads to organ dysfunction and if left untreated, leads to MODS and increased morbidity and mortality. It thus appears logical to resuscitate these patients with oxygen, fluids and cardiovascular support so that organ perfusion is restored and MODS (and its consequences) avoided. This resuscitation strategy was placed on a proper physiological footing by work of Shoemaker and colleagues, who in mid 1980s demonstrated that resuscitation by administration of oxygen, fluids and pharmacological support of cardiovascular system (mainly by inotropes like dobutamine) resulted in increased cardiac output, improved oxygen delivery to the tissue (increasing tissue oxygen consumption) and reduced mortality in complex surgical patients. Subsequently, Edwards et al showed that applying these ‘survivors’ parameters’ to patients in septic shock reduced mortality in that condition. Many subsequent studies demonstrated that this ‘strategy of goal directed therapy GDT’ did reduce mortality, however almost all studies included only a small number of patients. Not long after, some randomised controlled studies showed that this GDT and pushing oxygen transport to supra-normal values had little impact on mortality and may actually increase it. Improvement in mortality shown in earlier studies may well have been timely attention to detail in resuscitation and fluid therapy and early antibiotic use especially in sepsis/septic shock. Soon, pulmonary artery floatation catheters which had played a major role in management of patients with GDT (as cardiac output and oxygen transport were easily measured by these catheters) came under a ‘scientific’ cloud and, as their use was discouraged (for wrong reasons in author’s opinion), GDT died an untimely death.

Early Goal Directed Therapy for Sepsis:

Our understanding and knowledge of pathophysiology of critical illness, especially sepsis increased in the last decades of 20th century; unfortunately, this increased knowledge has not translate into improved survival. EGDT was ‘resuscitated’ by seminal work of Emmanuel Rivers and colleagues in 2001 showing that ‘early resuscitation’ in severe sepsis/septic shock improved mortality. This protocolised therapy, aiming for certain resuscitation goals, was named ‘Early Goal Directed Therapy’ (EGDT) for sepsis by these authors and briefly consists of:

- An initial fluid bolus (500 ml crystalloid or colloid) to achieve a central venous pressure (CVP) ≥8mmHg-12mmHg.
- Central line placement (with measurement of central venous oxygen saturation – ScvO₂).
- Vasopressors (if mean arterial pressure, MAP of ≤65 mmHg) or vasodilators if MAP ≥ 90mmHg.
• Use of inotropes (usually dobutamine) to achieve a venous oxygen saturation (ScvO\textsubscript{2}) of >70%.
• Failure to achieve this, use of blood transfusion or red cells to a packed cell volume (PCV) of 30%.
• Lactate measurement and achieving lactate reduction.
• Antibiotics.

All these are to be achieved in first 6 hours in the emergency department with subsequent admission to a place of higher level of care viz. ICU. EGDT for sepsis was endorsed and recommended by Surviving Sepsis Campaign (SSC) in their ‘6 hour resuscitation bundle’ (2004, 2008 and 2012). With the SSC endorsing EGDT for sepsis, this approach became the ‘norm’ by which many ICUs’ performance began to be judged! However, controversies about this approach were voiced almost from the beginning and these voices have recently gained more impetuous with publication of recent 3 randomised controlled trials.

What is the scientific basis of EGDT and what are the controversies that have arisen? Is there any scientific substance in these controversies? Given the controversies should we now abandon EGDT or continue to follow it? This brief review will try and address these issues in the following passages with appropriate minimum detail for the sake of brevity.

1. **There is very ‘thin’ scientific basis for EGDT for sepsis.** EGDT for sepsis become a standard care and management of sepsis and septic shock globally, especially after endorsement by SSC in their ‘6 hour sepsis bundle’. EGDT showed a significant mortality reduction in the treatment group (33.3% versus 49.2%; \( p = 0.01 \)). However, it was a single centre, unblinded study with a small number of patients (\( n=288 \) of which 25 were excluded from the final analysis). A Chinese study\textsuperscript{12} is referenced by SSC as evidence in support of EGDT for sepsis. However, there is no English translation available and therefore its claims cannot be verified. A meta-analysis published in 2013 identified 4 randomised control trials (RCTs) and 18 observational studies on EGDT for sepsis\textsuperscript{13}; there was no difference in mortality observed in RCT but with observational studies ‘a statistically significant ‘odds of surviving with 6 hour bundle care’ as against control (odds ratio 0.58; 95% CI 0.51-0.67; \( p<0.0001 \))’ was demonstrated. However, most of these before and after studies were uncontrolled and/or retrospective studies. Many of these observational studies have been cited by SSC as further supportive proof of EGDT for sepsis stating that ‘a large number of other observational studies using this form of early resuscitation have shown significant survival benefit compared to historical institutional controls’. Data and conclusions from observational studies should be adopted with caution.

2. **Targeted CVP is an arbitrary figure with no physiological basis.** A target level of CVP of \( \geq 8 \) mmHg but \( \leq 12 \) mmHg lacks scientific validation. First of all, CVP does not reflect left ventricular filling pressure, especially in sepsis\textsuperscript{14}. There is evidence that targeting CVP without regard to patients’ clinical state can and does lead to fluid overload as the authors themselves admitted; moreover fluid overload is directly linked to increased mortality\textsuperscript{15,16}.

3. **What does a central venous oxygen saturation (ScvO\textsubscript{2}) of >70% indicate?** ScvO\textsubscript{2} of <70% is suggested as evidence of organ hypoperfusion in Rivers et al\textsuperscript{7} study. In this context it is ‘equated’ with mixed venous oxygen saturation (SvO\textsubscript{2}). There are differences in blood contained in the superior vena cava (mostly coming from brain) and that found in the pulmonary artery (from where SvO\textsubscript{2} is measured). Moreover, it has been shown that ScvO\textsubscript{2} cannot be used as a substitute for SvO\textsubscript{2} in the critically ill\textsuperscript{17} and in cardiac surgery patients\textsuperscript{18}; especially in low cardiac output states, the very physiological abnormality low ScvO\textsubscript{2} attempting to diagnose. There is no certainty that increasing ScvO\textsubscript{2} will reduce lactate.

4. **Transfusing blood for a PCV of <30 does not improve outcome in sepsis.** Blood transfusions for a haemoglobin of >70g/1(7g/dl) have been shown to be of little benefit and
may well cause harm\textsuperscript{10,19} nor do they reduce lactate of increase ScvO\textsubscript{2}\textsuperscript{21}. A recent randomised trial in this regard has shown no mortality benefit is sepsis patients with blood transfusion\textsuperscript{10}.

5. 	extbf{Dobutamine infusion may not achieve increase in tissue perfusion and may be harmful.} Use of dobutamine to increase oxygen delivery (DO\textsubscript{2}) and oxygen consumption (VO\textsubscript{2}) is not necessarily without harm\textsuperscript{4,22}. Besides, ‘calculated’ increases in DO\textsubscript{2} and VO\textsubscript{2} need measurement of cardiac output, something not done in Rivers et al study.

There are a whole lot of other minor but significant points that make EGDT for sepsis questionable. In the original article by Rivers et al\textsuperscript{7} there is hardly any mention of oxygen as initial step in management; it is mentioned only in passing. Ventilation, sedation (and paralysis) is mentioned as a ‘step’ in management if ScvO\textsubscript{2} cannot be improved with above measures. Ventilation is not without risk and may well cause further hypotension with use of sedative agents. The EFDT pathway mentions cardiac index, and VO\textsubscript{2}, neither of which has been (or could be) measured in the trial! So why have Rivers et al\textsuperscript{7} mentioned it? And the original protocol mentions antibiotics but last of all. Experience and the literature have shown that if any strategy works in sepsis, it is early use of antibiotics!

So, should we abandon EGDT for sepsis? The answers are not easy. Early resuscitation is important in severe sepsis/septic shock; however, it needs to be tailored to each patient’s need. Antibiotics certainly are life-saving in severe sepsis/septic shock. EGDT may also have been of educational value in that the clinical community is much more aware of early treatment of sepsis. This may well be its greatest contribution to the wellbeing of sepsis patients and their improved survival.

References:

12. Early goal-directed therapy collaborative group of Zhejiang Province: the effect of early goal-directed therapy on treatment of critical patients with severe sepsis/septic shock: a


