An Exploration of the role of Early Goal Directed Therapy in Sepsis

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Abstract
Sepsis is one of the most commonly encountered scenarios in critical care medicine. In spite of massive advances in critical care, the incidence and mortality burden of sepsis remains quite high. Resuscitation of septic patients is one of the most researched topic in modern day medicine. Sepsis resuscitation was initially influenced by observation of supra-normal survivor values generating the idea of goal directed therapy. Subsequent studies resuscitating septic patients to these supra-normal values revealed no benefit and possible harm in this strategy. In order to resolve this issue, early resuscitation of septic patients to fixed haemodynamic goals at the most proximal point of disease process was proposed in 2001 and was named 'early goal directed therapy'. The study demonstrated a significant mortality benefit compared to usual care. This promising result led numerous trials to be conducted to test the hypothesis. Finally, after years of controversy, three large, multicentre trials were conducted in order to reach a conclusion and their results have recently been published. With the background of these recent changes, this review was conducted to describe the changes in 'early goal directed therapy' with time and to assess the available evidence guiding its use, specially focusing on the large new trials. This review also briefly outlines the pathophysiology of septic shock, describes the historical background of early goal directed therapy, and assesses the evidence regarding goal directed therapy in other physiological insults. To achieve these objectives, an extensive search in PubMed and general databases such as Google and Google scholar was carried out for published works. Studies were considered eligible for inclusion if they were randomised, controlled trials comparing early goal directed therapy to usual care in resuscitation of septic patients. After quality assessment of the selected studies, four studies were considered eligible to be included in the literature review. Analysis of these trials showed early goal directed therapy has no mortality benefit over patients receiving usual care. The analysis also revealed that the beneficial effects of early goal directed therapy in organ dysfunction could not be replicated in the newer three trials. Another important finding was that early goal directed therapy was not found to be cost effective. However, it should be taken into consideration that tremendous advance has occurred in critical care practice within the interval from the original trial to the publication of these newer trials and some components of the protocolised care may have been incorporated in routine care of septic patients. Contrary to these findings in patients with septic shock, goal-directed therapy has shown some promise when implemented in the peri-operative period. One large study along with meta-analysis revealed a lower incidence of morbidity and complications in patients treated with goal directed therapy compared to patients receiving usual care. However, no mortality benefit was demonstrated between the two groups. Overall, the publication of these new trials have made it evident that strict adherence to goal-oriented protocol is unlikely to be more beneficial and usual care based on good critical care practice should be the employed in sepsis resuscitation.

Keywords: Physiological, Findings, Usual

Introduction
There has been some dispute about agreeing on a definition of sepsis. Researchers have described 'severe sepsis' and 'septic shock' as separate entities in the sepsis-multiple organ dysfunction syndrome continuum. The current definitions are based on the Surviving Sepsis Campaign guidelines published in 2012.

Sepsis

Sepsis refers to the presence (probable or documented) of infection together with systemic manifestations of infection. In 1991, Bone suggested a set of definition based on the combination of a clinically diagnosed infection and measures of organ dysfunction. These 'Bone criteria' were of little practical value at the bedside but, crucially, provided a standardised set of diagnostic criteria that were used both in epidemiological surveys and as entry criteria for interventional studies. Later, this criterion was adopted by the American College of Chest Physicians and Society of Critical Care Medicine.

The internationally accepted definition was outlined during a conference held in 2001 and 2003 and retained the essential elements that Bone suggested. It requires a specific set of physiological and laboratory indices associated with a clinical suspicion of new onset of an infection as the source of the abnormalities. The diagnostic criteria for sepsis according to the Surviving Sepsis Campaign is given in the following table:

Table 1: Definition of Sepsis

Infection, documented or suspected, and some of the following:
General variables: • Fever (>38.30C) • Hypothermia (core temperature <360C) • Heart rate >90/min or more than two SD above the normal value for age • Tachypnea • Altered mental status • Significant oedema or positive fluid balance (>20 ml/kg over 24 hours) • Hyperglycaemia (plasma glucose >140mg/dl or 7.7mmol/L) in the absence of diabetes
Inflammatory variables: • Leukocytosis (WBC count >12,000/µL) • Leukopenia (WBC count <4000/µL) • Normal WBC count with greater than 10% immature forms • Plasma C-reactive protein more than 2 SD above the normal value • Plasma procalcitonin more than 2 SD above the normal value
Haemodynamic variables: • Arterial hypotension (SBP <90 mm Hg, MAP <70 mm Hg, or an SBP decrease >40 mm Hg in adults or less than 2 SD below normal age)
Organ dysfunction variables: • Arterial hypoxaemia (PaO2/FiO2 <300) • Acute oliguria (urine output <0.5 ml/kg/hr for at least 2 hrs despite adequate fluid resuscitation) • Creatinine increase > 0.5 mg/dl or 44.2 µmol/L • Coagulation abnormalities (INR > 1.5 or aPTT > 60s) • Ileus (absent bowel sounds) • Thrombocytopenia (platelet count < 100,000/ µL) • Hyperbilirubinemia (plasma total bilirubin > 4mg/dl or 70µmol/L)
Tissue perfusion variables: • Hyperlactatemia (> 1mmol/L) • Decreased capillary refill or mottling

Severe Sepsis

The term "severe sepsis" was proposed in 1992 by an international consensus panel to describe instances in which sepsis is complicated by acute organ dysfunction. The current definition of severe sepsis is essentially the same. Now, severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. Sepsis induced hypotension is defined as a systolic blood pressure (SBP) <90 mm Hg or mean arterial pressure (MAP) <70 mm Hg or a SBP decrease > 40mm Hg or less than 2 standard deviations below normal for age in the absence of other causes of hypotension.

Table 2: Definition of Severe Sepsis

Severe sepsis = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output <0.5 ml/kg/hr for more than 2 hrs despite adequate fluid resuscitation
Acute lung injury with PaO2/FiO2 <250 in the absence of pneumonia as infection source
Acute lung injury with PaO2/FiO2 <200 in the presence of pneumonia as infection source
Creatinine >2.0 mg/dl (176.8 µmol/L)
Bilirubin >2 mg/dl (34.2 µmol/L)
Platelet count <100,000/µL
Coagulopathy (international normalized ratio >1.5)

Septic Shock

The term "septic shock" was coined by the same consensus panel. It refers to sepsis complicated by hypotension that is refractory to adequate fluid resuscitation.

Pathophysiology of Septic shock

Septic shock is the more advanced and dreaded stage in the sepsis continuum. Septic patients not diagnosed and treated earlier in the disease spectrum inevitably succumb to this stage and progress to develop multiple organ dysfunction syndrome (MODS). The mortality rate is very high once patients reach this stage as patients tend to be more resistant to the resuscitation efforts. Hence, most of the effort in sepsis resuscitation is aimed at early diagnosis and prompt initiation of treatment, to prevent progression to septic shock. A good understanding of the pathophysiology of septic shock is therefore integral in discussion of sepsis resuscitation.

Septic shock results when infectious agents or infection-induced mediators in the bloodstream produce haemodynamic decompensation. Septic shock is primarily a form of distributive shock and is characterised by ineffective tissue oxygen delivery and extraction associated with inappropriate peripheral vasodilatation despite preserved or increased cardiac output. Presence of cardiovascular dysfunction in sepsis is associated with a significantly increased mortality rate of 70% to 90% compared with 20% in septic patients without cardiovascular impairment.

Myocardial dysfunction in Septic Shock

The 'classic' cardiovascular signs seen with severe sepsis were first described by Waisbren in 1951. The description mentioned about hyperdynamic state with full bounding pulses, flushing, fever, oliguria and hypotension. He also described a second smaller group of patients who were pale, clammy, profoundly hypotensive with low volume pulses, and who appeared much more ill. This group may have been simply under-resuscitated, not having enough fluid in their circulation. However, soon it became apparent that some patients did not significantly increase their cardiac output in response to expansion of their circulating volume, pointing to some element of myocardial dysfunction. A study performed in fully resuscitated young patients with septic shock demonstrated significant reductions in both stroke volume and ejection fraction compared with non-septic control patients from ICU, even when their total cardiac output was normal. A similar study showed both regional and global abnormalities of left ventricular function in patients with sepsis, in the absence of pre-existing ischaemic heart disease. This myocardial depression was not due to myocardial ischaemia, as coronary blood flow and coronary sinus lactate levels were normal in patients with septic shock. A concept of myocardial depressant factor that circulated in septic patients was proposed. However, it still remains unclear what this factor is, or even if it is a single entity or not. A small uncharacterised protein has been described in animal experiments but there have been other candidates like NO, cyclic GMP, TNFα. Diastolic dysfunction due to myocardial oedema and reduced left ventricular compliance have also been proposed to take part in this myocardial depression.

Circulatory failure in Septic Shock

The predominant feature in peripheral circulation is vasodilatation. The release of endotoxin or pro-inflammatory cytokines initiates a cascade of cellular and mediator changes in sepsis. The corner stone of impaired homeostasis in sepsis is an inflamed microcirculation. It is clogged with microthrombi and leaks extensively and the central role in this microcirculatory dysfunction is in turn played by the endothelium. This is supported by the observation of circulating endothelial cells in patients with septic shock, pointing to widespread endothelial injury. It is damage to the endothelium that turns the usual water tight blood vessels into sieves allowing large amounts of protein rich fluid to leak into the subcutaneous tissues, causing extensive tissue oedema and intravenous dehydration. Activation of the coagulation cascade leading to intra-vascular thrombosis is also a result of the damaged endothelium that starts liberating pro-coagulant factors. Besides these alterations, the endothelium also fails to perform its regulatory functions, and its nitric oxide (NO) system is severely disturbed. There is a heterogenous expression of inducible nitric oxide synthase (iNOS) in the endothelium of different areas of organ beds. Areas that lack iNOS have less NO induced vasodilatation and become underperfused resulting in pathological shunting of blood flow.

The endothelium is not the only component of microcirculation to be altered. All other cellular components of the microcirculation also undergo deterioration during sepsis. Smooth muscle cells lining the arterioles lose their adrenergic sensitivity and tone. The red blood cells become more rigid thus increasing the blood viscosity. Also, it has been suggested that endothelial glycocalyx destruction occurs during endotoxemia, and this may participate in causing microvascular perfusion deficit.

NO is central to the peripheral vasodilatation observed in septic shock. NO is produced from L-arginine by nitric oxide synthase (NOS). Three main isoforms of this enzyme are recognised: a neuronal form which synthesises NO as a neurotransmitter; a constitutive (endothelial) form (cNOS) responsible for basic NO production, and an inducible form (iNOS), which is expressed after cytokine stimulation and sepsis. In health, cNOS is involved only in low-output NO pathways concerned with homeostasis e.g. matching blood vessel calibre to blood flow and it's activity is controlled by a negative-feedback mechanism. The iNOS is quite different to this. It is not normally present in significant quantities in the vessels; rather, it is expressed after stimulation with pro-inflammatory cytokines such as TNF-α, IL-1, IL-2, IL-6 and INF-γ, which are all part of the inflammatory cascade triggered by endotoxin. The iNOS is a high- output pathway, producing large quantities of NO, and is insensitive to feedback control. As NO is a powerful vasodilator, this excess amount of NO leads to systemic vasodilatation seen in septic shock.

The aforesaid cellular alterations in the microcirculation lead to impairment of all three functional elements of the microvascular network. The arterioles are hyporesponsive to vasoconstrictor and vasodilators despite the elevated levels of catecholamines, perfused capillaries are reduced in number, and venules are obstructed by the sequestered neutrophils. In the capillaries, besides a decreased density, there also occurs increased heterogeneity and an increase in the proportion of stopped and intermittently perfused capillaries. These changes were more severe in non-survivors. This shut-down of the vulnerable microcirculatory units in the organ beds promotes the shunting of blood and hence oxygen, from arterial to venous compartment leaving the microcirculation hypoxic, along with a decrease in oxygen extraction. The

local microcirculatory partial pressure of oxygen drops below the venous oxygen pressure. This has been termed the 'po2 gap' and is an indicator of the severity of functional shunting. The systemic manifestation of this pathologic shunting is seen as a deficit of oxygen extraction by tissues with an apparently normal delivery, and raised venous po2 and lactate levels. In addition, the blood flow regulation of microcirculation is severely disrupted.

Mitochondrial dysfunction in Septic shock

Sepsis induced organ dysfunction has been suggested to be at least in part due to mitochondrial dysfunction as a result of oxidative stress and which results in failure of energy production. The pathogenesis of mitochondrial damage as a result of sepsis is probably a complex series of events. Both nitric oxide and reactive oxygen species combined with the release of a variety of exacerbating inflammatory mediators can act to directly or indirectly influence mitochondrial function and energy production. Mitochondrial dysfunction has been shown in animal models of sepsis. Ultrastructural damage was seen in mitochondria from livers of patients who had died of severe sepsis. Altered mitochondrial redox state and antioxidant depletion associated with mitochondrial dysfunction and severity of organ failure were also reported. The link between sepsis and mitochondrial damage has been described in several reviews. Oxidative stress-mediated damage to mitochondria therefore appears to be fundamental to the pathophysiology of organ failure in sepsis. There is a suggestion that progressive improvement in mitochondrial respiration is associated with recovery of organ function in patients who survive sepsis.

Relationship of sepsis with oxygen delivery and consumption

In a human body, oxygen enters the lung alveoli at the beginning of inspiration. Once it reaches the alveoli of lung, it comes in contact with the blood in the pulmonary capillaries. This blood is low in oxygen and due to the concentration gradient, there is diffusion of oxygen from the alveoli into the blood. This oxygen is mostly bound to the haemoglobin present in the red blood cells and transported to the tissue level. At the tissue level, this oxygen gets released from the haemoglobin, and is passively diffused into cells. The cells then utilise this oxygen to generate energy by aerobic metabolism. This process of oxygen delivery and consumption gets considerably altered in sepsis.

Oxygen delivery and consumption in Septic Shock

In sepsis, an altered relationship is believed to exist (broken line DEF). The slope of maximum OER (DE vs AB), reflects the reduced ability of tissues to extract oxygen, and the relationship does not plateau as in the normal relationship. Hence consumption continues to increase (E-F) to 'supra-normal' levels of DO2, demonstrating so called 'supply dependency' and the presence of a covert oxygen debt that would be relieved by further increasing DO2.

A critical decrease in systemic oxygen delivery (DO2) is followed by an increase in the systemic oxygen extraction ratio (OER) and a decrease in central venous oxygen saturation (Scvo2) or mixed venous oxygen saturation (Svo2). This increase in OER is a compensatory mechanism to match systemic oxygen demands. When the limit of this compensatory mechanism (OER>50-60%) is reached, anaerobic metabolism ensues leading to lactate production. In this critical delivery dependent or hypodynamic phase, lactate concentrations are inversely related to DO2 and Scvo2/Svo2. This phase can occur with normal vital signs and is commonly referred to as "occult shock", where the patient outwardly appears less ill. As a result organ dysfunction and sudden cardiopulmonary collapse are complications associated with this phase if unrecognised or left untreated. This state predominantly characterises the early sepsis presentation and is an important distinction from previous unsuccessful sepsis resuscitation trials performed in the ICU setting. After adequate resuscitation, a hyperdynamic phase follows the hypodynamic phase. Compensated sepsis is characterised by an elevated Scvo2/Svo2 and normal lactate. Later, an elevated lactate and elevated Scvo2/Svo2 denote pathologic delivery independence and is associated with increased mortality. The failure to increase OER and thus increase systemic oxygen consumption (VO2) may be secondary to impairment of microvascular oxygen perfusion or mitochondrial dysfunction.

Goals and End Points of haemodynamic support in patients with Septic Shock

Early haemodynamic assessment on the basis of physical findings, vital signs, central venous pressure, and urinary output fails to detect persistent global tissue hypoxia. A more definitive resuscitation strategy involves goal-oriented manipulation of cardiac preload, afterload, and contractility to achieve a balance between systemic oxygen delivery and oxygen demand. End points used to confirm the achievement of such a balance (resuscitation end points) include normalised values for central venous pressure, mean arterial pressure, mixed venous oxygen saturation, and arterial lactate measurement. While some question the accuracy of CVP in assessing volume status, equivalent outcomes have been shown when compared to the pulmonary artery catheter for assessment of fluid status in acute lung injury.

Mixed venous oxygen saturation as a resuscitation end-point

The balance between tissue oxygen delivery and consumption can be assessed using venous oxygen saturation, either mixed (Svo2) or central (Scvo2). Mixed venous oxygen saturation has been shown to be a surrogate for the cardiac index as a target for haemodynamic therapy.

In cases in which the insertion of a pulmonary-artery catheter is impractical, venous oxygen saturation can be measured in the central circulation.

Multiple studies have compared Scvo2 with Svo2 showing that there is an absolute difference between the two sites. While there is a difference, the clinical utility of both sites is comparable and validated by outcome studies. In a multicentre study, Pope *et al*. found that the failure to reach a Scvo2 greater than 70% within the first six hours is associated with significantly increased (14%) mortality. Castellanos-Ortega *et al*. examined all of the sepsis bundle elements at 6 and 24 hours of sepsis and found that the attainment of an Scvo 2> 70% had the statistically most significant impact on survival than all other bundle elements.

In a meta-analysis examining five studies comprising over 11000 patients, it was shown that patients reaching this end-point were twice as likely to survive as patients without reaching this end-point. Further evidence exists showing that continuous Scvo2 monitoring is superior to intermittent monitoring.

Lactate as a resuscitation end-point

Jones *et al*. described lactate clearance as a valuable tool for haemodynamic optimisation. The employment of lactate levels of ≥ 4mmol/L as a marker of severe tissue hypoperfusion as a univariate predictor of mortality is supported by a number of studies. Nguyen *et al*. found that the clearance of lactate over the first six hours after presentation was associated with significant decrease in pro- and anti-inflammatory biomarkers, improved organ function and reduced mortality. This was based on previous investigations using lactate clearance over 24 and 72 hours in the ICU setting. In a prospective multicentre trial of EGDT implementation, Nguyen *et al*. showed that when patients received EGDT, the mortality reduction was further enhanced when retrospectively grouped by improving levels of lactate clearance. Jones *et al*. showed that lactate clearance is equivalent to Scvo2 using the EGDT algorithm in a noninferiority study. In an ICU based study, Jansen *et al*. showed that therapy guided by lactate monitoring every 2 hours resulted in significant mortality benefit, decrease in organ failure, duration of inotrope therapy, mechanical ventilation and length of stay in ICU. However, a normal lactate in isolation does not exclude the presence of tissue hypoperfusion. 20 to 50% of septic shock patients will never elevate lactate levels at presentation or during the clinical course and frequently develop multi-system organ failure. These observations indicate that using lactate and Scvo2 are complimentary end-points and not mutually exclusive.

Surviving Sepsis Campaign

The high mortality associated with sepsis and septic shock called for international collaboration. In order to incorporate the best evidence based practice worldwide and implement them as a standard of care, a global initiative was taken – the Surviving Sepsis Campaign.

Surviving Sepsis Campaign: What is it?

It was on 2002 when critical care experts agreed that co-ordinated action was needed to reduce the mortality from severe sepsis. The Surviving Sepsis Campaign was developed as a collaboration between the European Society of Critical Care Medicine, the International Sepsis Forum and the Society of Critical Care Medicine. A desire to reduce the mortality from sepsis by 25% over a 5 year period became known as the Barcelona Declaration. In March 2004, the Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock were published- which were subsequently updated in 2008 and 2012 Care bundles were created in collaboration with the Institute for Healthcare Improvement. The first bundle (the Resuscitation Bundle) comprised a set of tasks to complete within the first 6 hours following the identification of sepsis – as per the recommendations of Rivers trial.

In 2010, the Surviving Sepsis Campaign published results from its improvement programme, which concluded in December 2008. Data were reported for 15,022 patients from 165 sites across 30 countries and showed that 71.5% of patients presented with septic shock. Compliance with the Resuscitation Bundle rose over a 2 year period from 10.9% to 31.3% with mortality reducing over the same period from 37.0% to 30.8% ($p < 0.001$). These results, although limited by voluntary contribution of data, demonstrated that the use of a multifaceted improvement initiative was successful in changing sepsis treatment behaviour as demonstrated by a significant increase in compliance with performance measures.

Surviving Sepsis Campaign Recommendations

Since 2002, the Surviving Sepsis Campaign (SSC) has promoted best practice, including early recognition, source control, appropriate and timely antibiotic administration, and resuscitation with intravenous fluids and vasoactive drugs.

According to the surviving sepsis campaign, the recommendation is the protocolised, quantitative resuscitation of patients with sepsis-induced hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4mmol/L). This protocol is to be initiated as soon as hypoperfusion was recognized and was not to be delayed pending ICU admission. During the first 6 hours of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion is to include all of the following as a part of a treatment protocol:

- CVP 8-12 mm Hg
- MAP ≥ 65 mm Hg
- Urine output ≥ 0.5 ml/kg/hr
- Superior vena cava oxygenation saturation (Scvo2) or mixed venous oxygen saturation (Svo2) 70% or 65% respectively.

It is recommended that resuscitation should be targeted to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.

Methodology and Results

This portion of the literature review is dedicated to the methodology employed in conducting this review. The purpose was to identify relevant literature, research or published material in line with the objectives of this review to explore the currently available evidence guiding the use of early goal directed therapy in the septic patient. The search strategy and sources, results of the search along with a description of the included studies is mentioned in the following part.

Search Strategy and data sources

Once the concept of goal directed therapy emerged, the research work has been incessant. As mentioned previously, Shoemaker and colleagues showed significant benefits in resuscitating critically ill patients scheduled for surgery to supra-normal survivor values. After a period of controversy, two methodologically sound, randomised, controlled, trials by Hayes *et al*. and Gattinoni *et al*. revealed no benefit from resuscitating a heterogenous group of critically ill patients to these supra-normal values. In an effort to find out the reason for discrepancy between these studies, Rivers and colleagues proposed early administration of goal oriented resuscitation measures. Interestingly, the study demonstrated a significant mortality benefit in the treatment group and thus generated widespread interest in this new, attractive "early goal directed therapy". This new concept was tested worldwide by numerous clinical trials. Reviewing all these evidence is out of scope for this literature review. Therefore, this review only focuses on the randomised, controlled, trials published comparing early goal directed therapy to usual care in sepsis resuscitation. An extensive computerised literature search of electronic database of PubMed and general databases such as

Google and Google scholar was performed. The titles and abstracts of all articles generated by the search were studied to identify the potentially relevant ones. The reference list of all the identified articles were also searched for additional published work.

Inclusion and Exclusion criteria

A set of inclusion and exclusion criteria were set for selection of studies. Only prospective, randomised, controlled, trials comparing early goal directed therapy vs usual care in patients with sepsis were considered eligible for inclusion. The definition of early goal-directed therapy was based on the original publication by Rivers *et al*. (the protocol is included in Appendix

1) Studies reporting only physiological end-points, solely descriptive or non-randomised studies, and studies conducted on paediatric population were excluded. The search process was confined to published work in English language only. Also, filters were used to sort out human studies only. As most of the work regarding early goal-directed therapy was undertaken after 2000, the search for studies was limited to the time period from 1 January 2000 up to 31 July 2015.

Assessment for feasibility and quality

The search strategy yielded 14 randomised controlled trials about early goal directed therapy. These trials were screened for appropriateness by filtering through two eligibility screens. The first filtration excluded the trials which were not relevant to the inclusion criteria. The second filtration assessed the quality of these trials to extract the best available evidence. For the purpose of this review, the quality assessment tool used by the author had the following components: randomisation, use of original EGDT protocol described by Rivers and colleagues, adherence to protocol, completion of study, losses to follow-up, and intention-to-treat analysis.

Results

The first screening of the 14 trials resulted in exclusion of 9 trials (Appendix 2). The reason for exclusion was not meeting the inclusion criteria of comparing EGDT to usual care. The remaining 5 trials were assessed for their quality against the quality assessment tool. This led to further exclusion of 1 trial (Appendix 2) due to it's use of a simplified severe sepsis protocol instead of the use of original EGDT protocol of Rivers trial and early stoppage of study before completion.

After assessment of feasibility and quality, only four trials were considered appropriate to be included in the review. Based on the components of quality assessment tool, they were judged to be of good quality.

Table 3: Methodological Quality of Included Studies

Study	Random- isation	Use of original EGDT protocol	Adherence to protocol	Completion of study	Losses to follow-up	Intention- to-treat analysis
Rivers *et al*., 2001	Yes	Yes	Perfect	Yes	No	Yes
ProCESS, 2014	Yes	Yes	High	Yes	No	Yes
ARISE, 2014	Yes	Yes	High	Yes	1 patient revoked consent, 2 patients were lost to follow- up	Yes
ProMISe, 2014	Yes	Yes	High	Yes	8 patients withdrew consent	Yes

Description of included studies

Rivers trial

The studies by Hayes *et al*. and Gattinoni *et al*. put a stop to unselectively aiming for survivor values when patients were admitted to intensive care unit. These 2 studies did not justify a more conservative approach, rather they emphasized the importance of adequate volume replacement, maintenance of blood pressure, and the use of moderate doses of inotropic drugs to maintain a normal cardiac output. A paper by Hinds and Watson highlighted the initiation of resuscitation at an early stage as the reason behind success of Shoemaker trial.

The authors considered the initial period of systemic inflammatory response syndrome as the 'golden hours', after which, transition to severe sepsis and septic shock occurs; hence resuscitation strategy was to be directed at that early stage to acquire maximum benefit. They suggested, for patients requiring operative care or for polytrauma patients, the pre-operative or early preventive optimisation of haemodynamic values should be the goal. However, in patients with septic shock, respiratory failure, pancreatitis where a delay after the initial insult couldn't be avoided, aggressive inotropic support to attain survivor values could be harmful.

Based on this rationale, Emanuel P. Rivers and colleagues conducted a trial, resuscitating critically ill patients immediately after presentation to the emergency department. It was a single centre, parallel-group, prospective, randomised, controlled trial performed from March 1997 to March 2000 in Detroit, USA. The study evaluated the efficacy of early goal directed therapy in emergency department as compared to the normal therapy, prior to admission in the intensive care unit. The population studied included patients who came to the emergency department with severe sepsis or septic shock. The criteria for inclusion were fulfilment of 2 out of 4 criteria for the systemic inflammatory response syndrome (SIRS) and a systolic blood pressure ≤ 90 mmHg (after a crystalloid-fluid challenge of 20-30 ml/kg over a 30-minute period) or a blood lactate concentration ≥ 4 mmol/L. 263 patients meeting the inclusion criteria were included in intention-to-treat analysis and randomised to receive either 6 hours of early goal-directed therapy or standard therapy (as a control). The baseline characteristics of the patients in both arms were similar, including vital signs, resuscitation end points, organ-dysfunction scores, and coagulation-related-variables.

Early goal directed therapy (EGDT) protocol consisted of several sequential goals started in the emergency department and continued for 6 hours:

- Central venous pressure 8-12 mmHg, achieved with fluid boluses
- Mean arterial pressure > 65 mmHg, achieved with vasopressors or vasodilators if necessary

- Scvo2 >70%, achieved with packed RBC transfusions to maintain Haematocrit > 30%. If Scvo2 target still not achieved, then dobutamine started at 2.5 mcg/kg/min (up to a maximum 20 mcg/kg/min)
- Urine output > 0.5ml/kg/hr
- Patients in the EGDT group underwent continuous monitoring of central venous oxygen saturation. After 6 hours, they were transferred to the first available inpatient beds. Monitoring of central venous oxygen saturation was then discontinued and care was handed over to critical-care clinicians. The treating physicians were unaware of the patients' study- group assignments.
- Standard therapy maintained:
- CVP 8-12 mm Hg
- Urine output > 0.5ml/kg/hr
- MAP 65-90 mm Hg with either vasopressors or vasodilators

Patients in the standard therapy group were treated at the clinicians' discretion, maintaining the aforementioned parameters, and were transferred to inpatient care as soon as possible.

The primary outcome was in-hospital mortality. Secondary outcomes were the resuscitation end points, organ-dysfunction scores, coagulation-related variables, administered treatments, and the consumption of health care resources. Of the 263 enrolled patients, 130 were randomised to EGDT arm and 133 to the standard therapy arm. In-hospital mortality was 30.5% in the EGDT group, as compared with 46.5% in the standard therapy group (p=0.009). A similar picture was seen for mortality at 28 days (p=0.01) and 60 days (p=0.03). Analysis of the deaths revealed rate of in-hospital death due to sudden cardiovascular collapse was significantly higher in the standard therapy group than in the EGDT group (p=0.02); rate of death due to multi-organ failure was similar in the 2 groups (p=0.27).

During the initial 6 hours, the combined haemodynamic goals for CVP, MAP and Urine output were achieved in 86.1% of patients receiving standard therapy, compared to 99.2% in the EGDT group (p<0.001). The patients in the standard therapy had a significantly lower central venous oxygen saturation (p<0.001) and a greater base deficit (p=0.006) than those assigned to EGDT; but, the 2 groups had similar lactate concentrations (p=0.62) and pH values (p=0.26).

During the interval from 7 to 72 hours, patients who received EGDT had a significantly higher mean (±SD) central venous oxygen saturation (70.4±10.7% vs 65.3±11.4%), a lower lactate concentration (3.0±4.4 vs 3.9±4.4 mmol/L), a lower base deficit (2.0±6.6 vs 5.1±6.7 mmol/L), and a higher pH (7.40±0.12 vs 7.36±0.12) than the patients assigned to standard therapy (p≤0.02 for all comparisons). During the same period, mean APACHE II, SAPS II, and MODS scores were significantly lower, indicating less severe organ dysfunction, in the patients assigned to EGDT than in those assigned to standard therapy (p<0.001 for all comparisons). Also, coagulation parameters like prothrombin time, fibrin split products and D-dimer concentration were all elevated in the standard therapy group compared with EGDT group (p<0.05 in all comparisons).

Regarding consumption of health care facilities, patients in the standard therapy group had stayed significantly longer in the hospital than the EGDT group (p=0.04). The study received several criticisms in the critical care community. It was a single centre study with questions arising about external validity. The emergency department staff were not blinded to treatment group. The mortality in the standard therapy group was higher than average, when compared to similar patients treated in other centres of the world. It was also impossible to determine whether one or all of the interventions were responsible for the reduced mortality. The use of packed RBC transfusions to increase Scvo2 was also controversial, considering all the transfusion hazards. Moreover, controversy stemmed from within the critical care and emergency medicine specialities as to the mechanism and execution of EGDT. Some emergency physicians expressed concern over the plausibility or necessity for emergency physicians to undertake the level of care required in the original trial as well as the availability of the technology required to follow Scvo2 trends.

PROCESS trial

Years of controversy about early goal directed therapy followed after publication of the Rivers study. Some physicians doubted the external validity of the study, whereas others were concerned with whether implementation of the protocol would be possible in the emergency setting. Carlbom *et al*. conducted a study to identify barriers to implementation of early goal directed therapy protocol in the busiest emergency departments in the United States. They found critical shortage of nursing staff, problems in obtaining central venous pressure monitoring, and challenges in identification of patients with sepsis as the largest roadblocks to implementing early goal directed therapy. Another study undertaken by Reade *et al*. demonstrated how doctors in emergency medicine, acute medicine and critical care in UK, USA and Australia & New Zealand approached initial resuscitative care of patients with severe sepsis. It found that only 0.1% doctors complied with all the Surviving Sepsis Campaign resuscitation recommendations. Differences persisted in reporting initial lactate measurement, fluid resuscitation, blood transfusion and insertion of invasive monitoring.

There was also controversy about whether one or all aspects of the protocol were responsible for the improved outcome.

To put an end to this controversy and reach an agreement, three collaborative, harmonised trials were started: one in the United States (ProCESS), one in the United Kingdom (ProMISe) and the other one in Australia and New Zealand (ARISE).

Protocolised Care for Early Septic Shock (ProCESS) was the US trial. It was a multicentre, randomised, controlled trial conducted between March 2008 and May 2013 at 31 hospitals. The purpose of the study was to test whether protocol based resuscitation was superior to usual care and whether a protocol with central haemodynamic monitoring to guide the use of fluids, vasopressors, blood transfusions, and dobutamine was superior to a simpler protocol that did not include these elements. The population studied included patients suspected of sepsis according to treating physician, ≥ 18 years of age, met 2 or more criteria for SIRS, and who had refractory hypotension (SBP < 90mmHg or required vasopressor to maintain 90mmHg after an I/V fluid challenge) or a serum lactate level ≥ 4mmol/L. The patients were randomly assigned in a 1:1:1 ratio to one of three groups: protocol-based EGDT, protocol-based standard therapy, or usual care.

Protocol-based EGDT group were treated according to a

protocol similar to the Rivers protocol; placement of a central venous catheter for CVP and Scvo2 measurement guided administration of intravenous fluids, vasopressors, dobutamine, or packed red-cell transfusions. Protocol-based standard therapy group also received a similar protocol based treatment, but the components were less aggressive and it did not require placement of a central venous catheter or blood transfusions. The protocol was created on the basis of review of literature, surveys and consensus feedback. Patients were resuscitated with fluids and vasopressors to reach goals for systolic blood pressure and shock index. The usual care group received treatment as per the bedside physician's discretion, with the study coordinator collecting data but not prompting any actions.

The primary outcome of the study was the rate of in-hospital death from any cause at 60 days. Secondary outcomes considered were death from any cause at 90 days, cumulative mortality at 90 days and 1 year, duration of acute cardiovascular failure, acute respiratory failure, acute renal failure, duration of stay in hospital and ICU, and hospital discharge disposition.

Among the 1341 patients included in the trial 439 were in the protocol-based EGDT group, 446 were in the protocol-based standard-therapy group, and 456 in the usual care group. The three groups were well matched at baseline with respect to demographic and clinical characteristics, as well as the care received before randomisation. Adherence to the protocol was high in both the protocol-based groups, incomplete adherence being 11.9% in the EGDT group and 4.4% in the standard-therapy group.

The 60-day in-hospital mortality for the combined protocol-based groups (19.5%) did not differ significantly from that in the usual-care group (relative risk 1.04; 95% confidence interval 0.82 to 1.31; p=0.83), nor did mortality differ significantly when the groups were compared separately (p values ranging from 0.31 to 0.89). There were also no significant differences in 90-day mortality or in the time to death up to 90 days and 1 year (p=0.66 for 90-day mortality and p=0.70 and p=0.92 for cumulative mortality at 90 days and 1 year, respectively).

The incidence of acute renal failure, as indicated by new need for renal replacement therapy, was higher in the protocol-based standard therapy group than in the other two groups (p=0.04), although the duration of therapy did not differ significantly across the groups. There were no significant between-group differences in the length of hospital and ICU stay, duration of cardiovascular or respiratory failure, hospital discharge disposition. Reports of potentially serious adverse events were rare and did not differ significantly across groups.

The trial concluded finding no significant advantage with respect to mortality or morbidity of protocol-based resuscitation over bedside care that was provided according to the treating physician's judgment. Also, no significant benefit was observed from use of central venous catheterisation and central haemodynamic monitoring.

The trial was well designed, pragmatic. Methods and statistical analysis were robust. It also recruited adequate number of patients as needed for 80% power to detect 6-7% mortality reduction with alpha 0.05. However, there were some limitations. The study changed the fluid resuscitation strategy mid-trial. Still, the mean volume of bolus administered fell within the range used in the study by Rivers *et al*. (20-30 ml/kg). Mortality was around 20% in the trial whereas initial power calculation was based on a mortality of 30-46%. Therefore, interim adjustment had to be made and recruitment target re-adjusted. Adherence to protocol was high, but not perfect and may be the reason behind difference with the findings of the Rivers study, where adherence to the protocol was perfect. The trial had limited power to address whether particular strategies were more effective in specific subgroups. Also, the in-hospital mortality found in this trial could have been influenced by practices regarding withdrawal of life support.

ARISE trial

This was one of the other three collaborative, harmonised studies, along with ProCESS trial of US and ProMISe trial of UK; a multicentre Australasian Resuscitation In Sepsis Evaluation (ARISE) study to test the hypothesis that EGDT, as compared with usual care, would decrease 90-day all-cause mortality among patients presenting to emergency department with early septic shock. The study was a prospective, randomised, parallel-group trial conducted from October 5, 2008 to April 23, 2014 in 51 tertiary care and non-tertiary care metropolitan and rural hospitals. Centres were located in Australia, New Zealand, Finland, Hong Kong, and Ireland.

The population studied included patients over 18 years who met the eligibility criteria within 6 hours after presentation to emergency department. Eligibility criteria were similar to ProCESS trial. Randomisation was done within 2 hours of fulfilment of inclusion criteria to 2 groups: EGDT group and control group. Antimicrobial drugs were started before randomisation. For patients in usual-care group, Scvo2 measurement was not permitted during the 6-hour intervention period. In the EGDT group, a protocol similar to the protocol in the Rivers study was used.

The primary outcome was death from any cause within 90 days after randomisation. Secondary and tertiary outcomes included survival time from randomisation to 90 days, mortality in the ICU, mortality at 28 days, in-hospital mortality at 60 days, cause-specific mortality at 90 days, length of stay in the emergency department, ICU, or elsewhere in the hospital, duration of mechanical ventilation, vasopressor support or renal replacement therapy, destination at the time of discharge, and adverse events.

The final cohort included 1588 patients. Of them, 792 were assigned to the EGDT group and 796 to the usual-care group. Demographics and clinical characteristics at baseline were similar in both groups. Patients in the EGDT group received a larger mean volume of intravenous fluids in the first 6 hours after randomisation than did those in the usual-care group and were more likely to receive vasopressor infusions, red-cell transfusions and dobutamine (p<0.001 for all comparisons). At 90 days after randomisation, mortality in the EGDT and usual-care group were similar (18.6% vs 18.8%, p=0.90). There were no significant difference in survival time, in-hospital mortality, duration of organ support, or length of hospital stay.

The study was methodologically sound. Adherence to the protocol was very high. The loss to follow-up was minimal. The statistical analysis plan was published prior to recruitment, thus eliminating the potential for analytical bias. The results also had a high degree of external validity, since participating sites were spread out across Australia and New Zealand, and included both metropolitan and rural centres. The rate of death was once again lower than the Rivers study.

The investigators commented that bias in small, single-centre trials may lead to inflated effect sizes that cannot be replicated in larger, multicentre studies. The study results were in concordance with the ProCESS study: no added benefit of EGDT over the usual resuscitation practice in patients presenting to emergency department with early septic shock.

ProMISE trial

The last one of the three harmonised trials was the ProMISe trial. It was a pragmatic, open, multicentre, parallel-group, randomised, controlled trial with an integrated cost-effectiveness analysis in 56 NHS hospitals in England from February 2011 to July 2014. The inclusion criteria for the population were similar to the other 2 trials. Patients were randomised within 2 hours of meeting inclusion criteria to EGDT or usual care in a 1:1 ratio. Antimicrobial drugs were started before randomisation. Blinding to study-group assignment was not done. After randomisation, the usual-care group continued to receive treatment as per the clinicians' discretion, whereas EGDT group followed a resuscitation protocol. Date were collected prospectively for the EGDT group and retrospectively for the usual-care group to avoid influence of data collection on treatment delivery.

The primary outcome was all-cause mortality at 90 days. Secondary outcomes were SOFA score at 6 and 72 hours; advanced cardiovascular, respiratory or renal support requirement; length of stay in emergency department, ICU, and hospital; duration of survival; all-cause mortality at 28 days, at hospital discharge, at 1 year; health-related quality of life, resource use, costs at 90 days and 1 year.

The final cohort included 1243 patients: 623 in the EGDT group and 620 in the usual-care group. The two groups were well matched at baseline. 90 day mortality was 29.5% in the EGDT group and 29.2% in the usual-care group (p=0.90). The EGDT group received more intense treatment as indicated by increased use of intravenous fluids, vasoactive drugs, and red-cell transfusions. They also had significantly worse organ-failure scores, more days receiving advanced cardiovascular support, and longer stays in the ICU. On average, EGDT increased costs, and the probability that it was cost-effective was below 20%.

Table 4: Summary of the included trials

Study	Study population	Study design	Study size	Treatment regimen	Primary outcome	Secondary outcome
Rivers *et al*. 2001	Patient with fulfilment of 2 of 4 criteria for SIRS and SBP<90mmHg (despite fluid therapy)or lactate>4mmol/l	Single centre, randomised, controlled, trial	263 patients (130 EGDT, 133 standard therapy)	Early goal directed therapy vs usual care	In- hospital mortality	Resuscitati-on end points, organ-dysfunction scores, coagulation-related variables, and the consumption of health care resources.
ProCESS , 2014	Patient with 2 or more criteria for SIRS and refractory hypotension or lactate>4mmol/l	Multi- centre, randomised, controlled, trial	1341 patients (439 protcol based EGDT, 446 protocol based standard therapy, 456 usual care)	Protocol based EGDT vs Protocol based standard therapy vs usual care	60-day in-hospital mortality	90-day mortality, cumulative mortality at 90 days and 1 year, duration of organ failure, duration of hospital and ICU stay, discharge disposition
ARISE, 2014	Patient with 2 or more criteria for SIRS and refractory hypotension or hypoperfusion	Multi- centre, randomised, controlled, trial	1600 patients (796 EGDT, 804 usual care)	Protocol based EGDT vs usual care	All-cause mortality within 90 days	Survival time from randomisation, mortality in ICU, mortality at 28 days, in- hospital mortality at 60 days, length of stay in ED, ICU, duration of organ support, discharge disposition, adverse events
ProMISe, 2015	Patients with 2 or more criteria for SIRS and refractory hypotension or hyperlactatemia	Multi- centre, randomised, controlled, trial	1260 patients (630 EGDT, 630 usual care)	Protocol based EGDT vs usual care	All-cause mortality at 90 days	SOFA score at 6 and 72 hours; duration of organ support in first 28 days; length of stay in ED, ICU, hospital; all- cause mortality at 28-days, discharge and 1 year; health related quality of life, resource use, cost at 90 days and 1 year

Discussion

Since the birth of early goal directed therapy, it has generated much controversy across the globe. The protocol has been tested time and time again in different emergency settings in different countries with varying results. This section of the review aims to critically appraise the currently available evidence identified by the methodology section and to highlight the similarities and differences in the results of the different trials comparing early goal directed therapy with usual care in resuscitation of septic shock. This section also briefly compares effects of early goal directed therapy in the setting of other physiological insults.

Effects of Early Goal Directed Therapy in Sepsis

Early goal directed therapy, as described first by Rivers *et al*. revolutionized septic shock resuscitation. The original study reported beneficial effects not only regarding mortality, but also regarding various haemodynamic parameters and organ function. The subsequent studies tested these aspects of the study individually as well as the cost-effectiveness of the proposed protocol.

Effects of EGDT on mortality

Prior to the Rivers study, resuscitation of septic shock was a fiercely debated topic. Those were times when slight hope to combat the high mortality of sepsis by treating high-risk patients to supra-normal values was taken away by subsequent trials showing possible danger in such strategy. The 16% mortality benefit reported by Rivers *et al*. therefore understandably generated considerable interest. The study included patients who were sicker than the previous studies, considering the haemodynamic parameters: with lower

central venous oxygen saturation and lower central venous pressure than those studied by Gattinoni *et al*. and with a higher lactate concentration than those studies by Hayes *et al*. Still, it managed to find significant mortality benefits in outcome compared to these previous studies: the in-hospital mortality in the study by Hayes *et al*. was 54% in the protocol group and 34% in the control group, the mortality in the control group, cardiac index group and oxygen saturation group were 48.4%, 48.6% and 52.1% respectively in the study by Gattinoni *et al*., compared to control group and EGDT group mortality of 46.5% and 30.5% respectively in Rivers study. The investigators were of the opinion that earlier recognition and administration of goal-directed therapy (EGDT) to optimise haemodynamic parameters was the reason behind this. The high numbers of sudden cardiovascular collapse in the standard therapy group indicated an abrupt transition to severe disease. Early identification and implementation of EGDT in patients with global tissue hypoxia but stable vital signs prevented this abrupt transition and thus contributed to the lower mortality. Aggressive haemodynamic optimisation and other therapy undertaken after the early hours was incompletely effective or even deleterious, as demonstrated by Hayes *et al*. After mixed results from numerous small, often methodologically flawed studies, the results of three harmonised, large, multicentre trials ProCESS, ARISE, and ProMISe were published. Interestingly, they failed to replicate the benefit showed by the Rivers trial. The mortality rates in both the control groups and the protocol groups were found similar in all three of these trials.

Although, the trials used similar inclusion criteria to the Rivers trial, the patient cohorts were slightly different. The cohort in the Rivers trial was slightly older, had higher rates of pre- existing heart and liver disease, and a higher initial serum lactate level compared to the cohorts of the newer three trials. Also, the Scvo2 values were measured before randomisation and initial fluid administration in the Rivers trial, whereas it was done after randomisation in the latter three- explaining the lower Scvo2 levels observed in the cohort of Rivers trial. Although it could be argued that the higher mortality benefit was observed due to the comparatively sicker cohort in the Rivers trial, the mortality benefit was absent even when the analysis was restricted to the sickest third of the patient in the ProCESS trial. The adherence to the protocol in the newer trials, although very high, were not perfect, as was the case in Rivers trial and hence could not be ruled out as the cause for the mortality difference among them. Also, of note is most of the study participants in these newer trials had received antibiotics prior to enrolment in the study, while for the Rivers study antibiotics were administered after enrolment. Early administration of antibiotics has been demonstrated to improve mortality in sepsis, and this administration of antibiotics prior to enrolment as a part of standard care in the emergency department could have led to the equivalence of mortality in the protocol and usual care arms in the newer trials.

Effects of EGDT on organ dysfunction

In the study by Rivers *et al*., the authors showed during the 7-72 hours period, the patients in the EGDT arm had a significantly higher mean central venous oxygen saturation, a lower lactate concentration, a lower base deficit, and a higher pH than the patients assigned to standard therapy ($p \leq 0.02$ for all comparisons). They also reported significantly higher APACHE II score, SAPS II, and MODS, prolonged prothrombin time, higher concentration of fibrin-split products and D-dimer in patients assigned to the standard therapy group compared to patients in the EGDT group ($p<0.001$ for all comparisons). The investigators projected that early goal directed therapy significantly reduced organ dysfunction in septic patients. However, like the effect on mortality, these beneficial effects of EGDT on organ function was once again found to be absent in the three newer trials. In the ProCESS trial, the incidence of acute renal failure was higher in the protocol-based standard therapy group, although the duration for renal replacement therapy was similar in all three arms. Regarding incidence of acute respiratory failure, acute cardiovascular failure, length of ICU stay and hospital stay, discharge deposition - no difference existed among the three groups. Similarly in the ARISE trial, there were no difference in the use and duration of invasive mechanical ventilation, renal replacement therapy, duration of ICU and hospital stay; although vasopressor support was used in significantly more number of patients in the EGDT arm ($p<0.001$). And finally in the ProMISe trial, the findings of the other two trials were replicated once again. The mean SOFA score at 6 hours, the proportion of patients who received advanced cardiovascular support, and the median length of stay in the ICU were significantly greater in the EGDT group than in the usual care group ($p<0.05$ for all comparisons). However, no differences existed with regards to provision of advanced respiratory support, renal support, and length of hospital stay.

Cost-effectiveness of EGDT

One of the controversies regarding the proposed EGDT protocol was whether it was cost- effective to provide such highly specialised care in the emergency setting. The recently published ProMISe trial included cost-effectiveness of EGDT as one of the secondary outcome measures of the study. It found that the mean EQ-5D scores and QALYs were similar in the two groups. The average cost was higher in the EGDT group (£12,414) than in the usual care group (£11,424), but the difference was not significant ($p=0.26$). The incremental net benefit for EGDT as compared with usual care was negative. The probability EGDT was cost-effective was below 20%.

Additional findings

There has been much debate regarding the individual elements (i.e. fluid resuscitation to a central venous pressure goal, transfusion to a haematocrit goal) of EGDT in improving mortality from sepsis. In a study conducted by Jones *et al*., it was shown that an EGDT protocol based on serial measurement of serum lactate levels was not inferior to an EGDT protocol that used Scvo2 monitoring. Following that study, the ProCESS and ProMISe trials also showed no significant benefit of the mandated use of central venous catheterisation and central haemodynamic monitoring in all patients.

In EGDT protocol driven resuscitations, fluid administration was guided by urine output and central venous pressure, while for the standard practice there was no defined endpoint for fluid administration. However, recent studies have demonstrated that central venous pressure is inaccurate in determining fluid responsiveness. Other modalities, such as echocardiographic measurements, arterial pulse pressure

variation, and passive leg raise have demonstrated a better ability to determine if a patient will respond to a fluid administration. In the Rivers study all patients enrolled had an arterial catheter and a central venous catheter placed, while in the newer three trials only the EGDT treatment group was mandated to have a central line. This significant difference in rate of central line insertion demonstrates that not only is a central line not needed for adequate resuscitation but that other markers beyond central venous pressure and Scvo2 monitoring can be used to guide resuscitation without causing an increase in mortality.

A similar criticism of the original EGDT study involves the blood transfusion strategy. Rivers and his colleagues argue in a 2006 CHEST review of EGDT that the blood transfusion goal is essential as 50.4% of patients who received red cell transfusion had improvement in their central venous oxygen saturation (Scvo2) to greater than 70% as compared to 35.9% who had fluid resuscitation alone. Several studies have looked at transfusion thresholds in diverse populations of critically ill patients, and they all demonstrate that a restrictive transfusion threshold (usually haematocrit $\geq 21\%$), offers a mortality benefit over a liberal threshold. Thus, it is no surprise that the newer three trials demonstrated that a standard practice approach demonstrated equivalence, in regards to mortality, when compared to protocol driven care with transfusions to a conservative transfusion threshold.

Conclusion and Recommendations

Since the publication of the Shoemaker trial, goal directed therapy generated considerable controversy over almost three decades. Trials after trials were conducted across the globe to resolve the issue and reach a concrete decision. The era following the Shoemaker trial was marked by two studies by Hayes *et al*. and Gattinoni *et al*. demonstrating possible harm in treating patients to supra-normal survivor values, as suggested by the Shoemaker trial in high- risk surgical patients. Despite the negative results of these trials, interest grew profoundly in the critical care community. This resulted in the publication of a landmark trial by Rivers and colleagues, generating the term 'Early Goal Directed Therapy', due to implementation of resuscitation care at the most proximal point of sepsis. The significant mortality benefit demonstrated in this study led to further trials, testing this hypothesis in larger settings. After numerous, small, sometimes methodologically flawed studies, three large, multicentre, harmonised, randomised, controlled trials were published recently to put an end to the issue. This review aimed to highlight these studies of different era and thus create a better understanding of early goal directed therapy from it's birth to it's current state.

After the publication of the three, new, large studies, it has become clear that using early goal-directed therapy protocol does not significantly improve mortality compared to usual care in patients admitted to emergency department with septic shock. Also, the beneficial effects of EGDT on organ dysfunction described in the study by Rivers *et al*. could not be replicated in the newer trials. Another issue which consistently came up since the EGDT protocol was proposed was the cost-effectiveness of using such specialised care. The newly published ProMISe trial showed that the probability that EGDT was cost-effective was below 20%.

Although the results of these newer trials fail to demonstrate any benefit of using EGDT over usual care, this does not spell the end of EGDT. If we try to find out possible reasons behind the discrepancy of the studies, a couple of points become evident. One of the probable explanations behind the difference in results is the evolvement of sepsis resuscitation care. Changes in the past decade in critical care, including use of lower haemoglobin levels as a threshold for transfusion, implementation of lung-protection strategies, and use of tighter control of blood sugar, may have reduced the overall mortality and the marginal benefit of the original resuscitation strategies. This is supported by the fact that in-hospital mortality for patients admitted to ICUs with severe sepsis and septic shock has been reduced by 1 percentage point per year during the past two decades. The difference in the mortality benefits can also be attributed to the fact that bias in small, single-centre trials may lead to inflated effect sizes that cannot be replicated in larger, multicentre studies, as shown by some previous studies.

Another section, this review aims to highlight is the use of goal directed therapy in the peri- operative period. A large, multicentre, recent trial published by Pearse and colleagues along with a meta-analysis show that goal directed therapy may be associated with lower rates of complications and morbidity in the post-operative period; however, no mortality benefit could be demonstrated.

Implications for practice and recommendations

Considering the results of this review, it is clear that the use of protocolised care for sepsis resuscitation has no significant benefit over the usual care. The newer trials demonstrated unanimously that fluid resuscitation based on central venous pressure and resuscitation based on continuous central venous oxygen saturation monitoring are cumbersome and devoid of significant advantages. Also, the risk-benefit ratio of a liberal transfusion strategy is controversial. It is therefore the recommendation of this review, that resuscitation of septic patients based on the usual care without the use of central venous oxygen monitoring, central venous pressure monitoring, liberal transfusion strategy is likely to be easier, cost-effective and more beneficial to the patient.

Conclusion

After almost three decades of conflicting evidence, sepsis resuscitation has finally received some conclusive evidence. The result of the three, harmonised, multicentre, randomised, controlled trials: ProCESS, ARISE and ProMISe reveal resuscitation of septic patients by early goal directed therapy is not superior to usual care with regards to mortality, organ dysfunction or cost-effectiveness. However, it must be pointed out that the advancement in critical care may be largely responsible for nullifying the mortality benefit observed in the study by Rivers and colleagues. Also, some part of the original protocol published by Rivers *et al*. may have been incorporated in the regular practice of sepsis resuscitation. Whether any individual element of the early goal directed therapy protocol was responsible for the mortality benefit observed in the Rivers' trial remains to be seen. Overall, it can be said that sepsis resuscitation has finally gained some conclusive evidence. But, there still remains some unresolved issues which may still prove useful for future practice.

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