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Early Sepsis Management

Jacqueline Pflaum-Carlson, MD
******@***hfhs.org

Resident - Henry Ford Hospital · Department of Emergency Medicine

Jayna Gardner-Gray, MD
******@***hfhs.org

Resident - Henry Ford Hospital- Department of Emergency Medicine

Gina Hurst, MD
******@***hfhs.org

Resident - Henry Ford Hospital- Department of Emergency Medicine

Emanuel Rivers, MD, MPH
******@***hfhs.org

Attending Staff, Emergency Medicine and Surgical Critical Care - Henry Ford Hospital

Sepsis is a recognised clinical spectrum of infection that often results in catastrophic physiologic and metabolic abnormalities. This article aims to identify the derangements associated with sepsis and to review the evidence-based literature.

The tenets of early sepsis management include diagnosis, risk stratification (elevated serum lactate or hypotension), assessment of haemodynamic response after a fluid challenge, antibiotics, source control and haemodynamic optimisation. Whether this combination of interventions is called early goal-directed therapy (EGDT), the resuscitation bundle (RB) or a standard operating procedure (SOP), mortality is improved when performed. Figure 1 (EGDT algorithm) on p.70 delineates how to carry out EGDT in the management of sepsis. We will discuss these treatments in the paragraphs to follow.

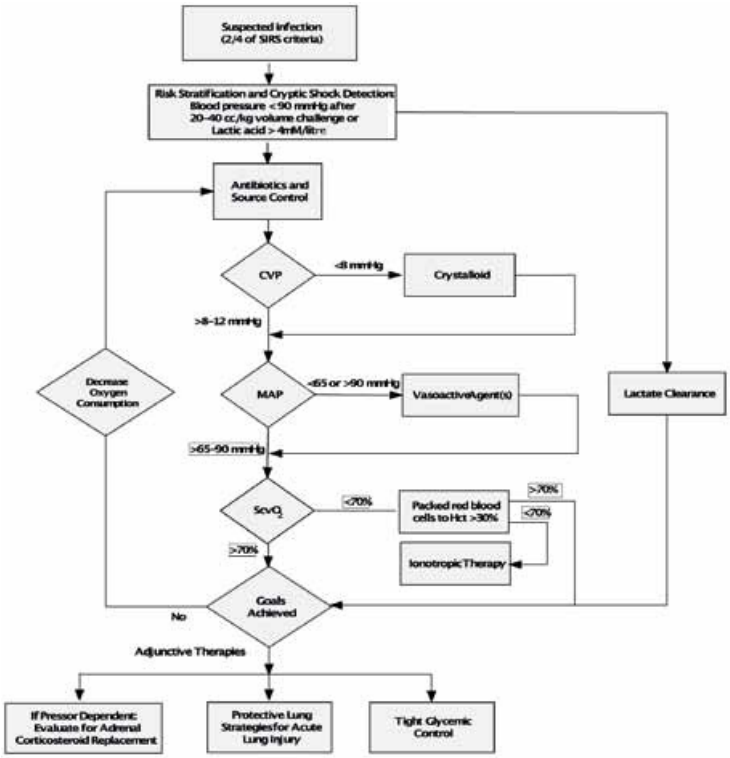

Figure 1 Algorithm of Early Goal-Directed therapy with Recommended Ancillary treatments

The incidence of sepsis is rising as patients who are at high risk are living longer with multiple co-morbidities. As a result hospitalisation for the diagnosis of sepsis is increasingly more common. Sepsis-associated mortality ranges from 15-49% (Angus et al. 2001), and contributes to nearly 17-40% of hospital deaths, making it the most lethal hospital admission diagnosis (Kumar et al. 2011). As the population continues to age, sepsis-related admissions are projected to continue to rise, making standardised approaches to the identification and treatment of sepsis imperative.

Early Detection or Screening for Sepsis

The systemic inflammatory response syndrome (SIRS) was developed as a clinical aid to direct the clinician to entertain the diagnosis of infection. It comprises two of the following four items: 1) temperature >38.3°C or <36.0°C; 2) heart rate >90 beats/min; 3) respiration rate >20 breaths/min or 4) white blood cell count >12,000 or <4000/mm3 , or >10% increased bands or immature cells (Bone 1985; Rangel-Frausto et al. 1995). The first use of SIRS for screening revealed that the more SIRS criteria, the greater degree of admission, increased length of hospital stay and costs (Tuttle 1996).

Antibiotic Therapy

The evidence for cultures and early and appropriate antibiotic administration is abundantly present in both animal and human studies of sepsis (Natanson et al. 1990). Bacteraemia is associated with an increased mortality, and this mortality may be increased up to five-fold in patients who receive inappropriate initial antibiotic therapy (Kang et al. 2012; Cardoso et al. 2010; Levy et al. 2010; Kumar et al. 2009). Mortality can increase up to 7.6% for each hour delay in antibiotic administration after the onset of hypotension or shock (Kumar et al. 2006; Ferrer et al. 2014).

Source Control

Source control is imperative and should be done as quickly as possible following initial resuscitation. The tenets of source control are appropriate radiographic imaging and interpretation, removal of the insult or a definitive surgical procedure. Every hour of delay from admission to surgery has been associated with an adjusted 2.4% decreased probability of survival or a 16% reduction in mortality if no source control within 6 hours (Bloos et al. 2014; Marshall and al Naqbi 2009; Buck et al. 2013). Patients who had surgical source control delayed for more than 6 hours had a significantly higher 28-day mortality (42.9% vs. 26.7%, $p < 0.001$); this delay was independently associated with an increased risk of death (Bloos et al. 2014; Dellinger et al. 2013b).

Risk Stratification (Lactate and Refractory Hypotension)

A hypotensive episode (systolic blood pressure less than 90 mmHg) is associated with an increased risk for death whether in the ED or inpatient unit (Jones et al. 2006; Lee et al. 2014). The discriminatory value of hypotension increases after a fluid challenge (Lee et al. 2014). If hypotension is not corrected by a fluid challenge, this portends early organ dysfunction, haemodynamic decompensation and increased mortality (Lee et al. 2014; Liu et al. 2013; Khalid et al. 2014). Ironically, paradoxical hypotension can be seen after fluid challenge (Lee et al. 2014b). Hypotensive ward patients who deteriorate further after initial stabilisation have a higher mortality (up to 42%, 28-day) and increased hospital resource consumption (Champunot et al. 2014; Khalid et al. 2014; McKinley et al. 2011). Hypotension refractory to fluids and requiring vasopressor therapy carries a mortality of 20 to 52% (Levy et al. 2010; Cannon et al. 2010; Durairaj and Schmidt 2008; Hilton and Bellomo 2012; Lee et al. 2012).

Weil and Aduen et al. established the prognostic value of a lactate greater than or equal to 4mM/L on hospital admission, which has been confirmed by multiple studies (Broder and Weil 1964; Cady et al. 1973; Aduen et al. 1994; Mikkelsen et al. 2009; Trzeciak et al. 2007; Shapiro et al. 2005; Pearse 2009). Whether central venous or arterial (Reminiac et al. 2012), increased lactate levels are associated with increased mortality (Puskarich et al. 2014; Howell et al. 2007). Clinical deterioration in patients with intermediate lactate levels (between 2.0 and 4.0 mmol/L) means that they are particularly at risk for mortality, as 22.7% will progress to sepsisinduced tissue hypoperfusion with an associated mortality of 10.1% (Hoon et al. 2012).

Lactate levels can be normal in septic shock and should be used with caution as a sole screening tool and endpoint (Singer et al. 2014; Dugas et al. 2012; Wacharasint et al. 2012; Cannon et al. 2013; Song et al. 2012). Blood lactate levels are not uniformly elevated in critically ill patients with liver disease, and levels above 2.2 mM/L are associated with increased mortality (Kruse et al. 1987). A normal shock index (heart rate/systolic blood pressure (<0.7) in patients presenting with a presumed infection indicates very low risk (high negative predictive value) for increased lactate levels (>4 mM/L) (Berger et al. 2013; Rady et al. 1994; Rady et al. 1996).

The Pathobiology of Haemodynamic Optimisation

Sepsis is a result of severe haemodynamic triggers that ultimately result in an imbalance between oxygen supply and demand. Based on this principle, EGDT sought to identify these abnormalities and aim for early correction and restoration of homeostasis. In light of a trilogy of recent publications comprising Protocolized Care for Early Septic Shock (ProCESS) (ProCESS Investigators et al. 2014), Australasian Resuscitation in Sepsis Evaluation (ARISE) (ARISE Investigators et al. 2014) and Protocolized Management in Sepsis (ProMISe) trials (Mouncey et al. 2015), this article aims to highlight the best practice recommendations for early sepsis management.

Preload Optimisation or Intravenous Fluids

Due to physiologic fluid shifts and fluid losses, septic patients are often volume depleted, and a minimum of 20-30ml/kg of fluid should be given. Following this initial bolus, infusion of intravenous fluids may be continued as long as the patient continues to improve haemodynamically. In regards to choice of fluid therapy, studies have shown that resuscitation with crystalloids, such as normal saline or lactated Ringer's or albumin, does not confer a reduced mortality in severe sepsis but may in septic shock (Rochwerg et al. 2014; Delaney et al. 2011). Albumin may be a considerable adjunct when patients require large amounts of crystalloid infusion (Caironi et al. 2014).

One of the benefits of aggressive fluid therapy is a reduction in vasopressor use during the first 6 hours. Early reduction in vasopressor therapy further reduces the need for vasopressin and corticosteroid use and may confer improved mortality (Waechter et al. 2014).

Preload Measurement (Central Venous Pressure or Other Surrogates)

A central venous pressure (CVP) of between eight and 12 mmHg is recommended to mitigate the circulatory insufficiency in the form of hypovolaemia and loss of vasomotor tone. Recent studies have called into question the value and necessity of CVP monitoring, due to inability to find a reliable relationship between blood volume and recorded CVP (Schmidt 2010; Marik and Cavallazzi 2013). Clinically the picture is often more complex than an isolated number, as coexisting conditions such as anaemia, myocardial suppression, mechanical ventilation, arrhythmias and vasopressor administration can play a role in falsely elevated or depressed values. CVP-guided fluid administration has been shown to decrease vasopressor therapy and in the early stages of sepsis has been shown to decrease mortality (Walkey 2013). On the contrary, aggressive fluid resuscitation in the late stages of the sepsis spectrum has been shown to increase morbidity, mortality and ventilator-dependent days (Murphy et al. 2009). In patients in whom central line placement is difficult or undesirable, bedside echocardiography, inferior vena cava measurements for respiratory variation, transoesophageal Doppler monitoring and stroke volume variation using arterial pulsation monitoring can be alternatives. However, clinical pitfalls exist with these modalities as well, and the clinical picture on the whole should be given greater weight than an isolated lab or mechanical value.

Afterload (Blood Pressure Target and Vasopressor Use)

Sepsis-associated vasodilatation and the loss of systemic autoregulation often necessitate administration of vasopressors (Dellinger et al. 2013a). Studies have shown that delays in restoration of physiologic blood pressure are related to increased mortality risk (Dunser et al. 2009; Beck et al. 2014). While increasing mean arterial pressure (MAP) above 65 mmHg has been associated with increased cardiac output, improved microvascular function and decreased blood lactate concentrations, there is substantial individual variation (Thooft et al. 2011). An individual's physiologic baseline and personal needs should be contemplated on a case-by-case basis; however, the recommended target mean arterial blood pressure is 65 mmHg (Varpula et al. 2005; Dunser et al. 2009; Asfar et al. 2014). Levy et al. have shown that the delayed use of vasopressor therapy for cardiovascular support is incrementally associated with a significantly higher mortality than any other organ failure beyond the first 24 hours (Levy et al. 2005).

There has been no demonstrable difference in the rate of death between patients treated with dopamine as the first-line vasopressor agent or norepinephrine; however, the use of dopamine has been associated with a greater number of adverse events (De Backer et al. 2010). Although studies have not shown outcome improvements with lowdose vasopressin, there is evidence that concomitant corticosteroid therapy may be beneficial (Russell et al. 2009; Gordon et al. 2014).

Initiation of vasopressor therapy should be done with caution, as it may be detrimental. Early initiation can falsely elevate CVP if started immediately after central venous line placement and prior to complete fluid resuscitation (Nouira et al. 2005). Thus the focus during the first hour should be aggressive fluid administration, only thereafter starting vasoactive agents, while continuing aggressive fluid administration (Waechter et al. 2014).

Central Venous Oxygenation

Central venous oxygenation (ScvO2) has the unique ability to demonstrate imbalances between oxygen delivery and oxygen consumption, and studies have repeatedly proven the utility and outcome benefit of this endpoint (Chamberlain et al. 2011). For instance, it has been shown that early ScvO2 can predict the difference between sepsis survivors and non-survivors and outcomes in acute lung injury after nearly 47 hours (Varpula et al. 2005). EGDT calls for action manoeuvres based on persistently low ScvO2 on the basis that therapies are necessary to either increase oxygen delivery or decrease venous oxygen consumption to prevent or limit tissue hypoxia, lactate generation and cardiopulmonary complications. Suggested goals for increasing ScvO2 involve fluid resuscitation, inotropic administration, red blood cell transfusion and decreasing systemic oxygen demands (early intubation). Although the trilogy of recent sepsis trials confer no mortality benefit of ScvO2 over usual care, recent studies show increased mortality and outcome benefits when ScvO2 is corrected (Boulain 2014; Levy et al. 2014).

Arterial Oxygen Content (Oxygen and Blood Transfusion)

Anaemia in sepsis is associated with an increase in both myocardial and systemic oxygen extraction rates accompanied by a compensatory increase in cardiac output. Anaemia can be multifactorial, and the underlying causation ranges from the dilutional effect of aggressive fluid resuscitation, bone marrow suppression, disseminated intravascular coagulation and the presence of pre-existing illness. Ultimately, the increase in myocardial oxygen consumption can lead to troponin elevations, increasing lactate levels, tachyarrhythmias and persistent hypotension. Targeting a pre-established 'optimal number' can be complicated as haemoglobin concentrations and requirements vary by organ, circulation

and co-morbidities. Prior transfusion-related studies have shown inconsistent data, with a recent study showing no significant difference in 90-day mortality, use of life support or ventilator-free days when a level of seven g/dL versus nine g/dL was targeted (Holst et al. 2014). Current recommendations aim to limit transfusions to patients with persistently low ScvO2 despite appropriate interventions based on the patient's clinical picture, including vital signs and known pre-existing conditions (cardiovascular disease).

	EGDT (Rivers et al. 2001)	ProCESS (ProCESS Investigators et al. 2014)	ARISE (ARISE Investigators et al. 2014)	ProMISe (Mouncey et al. 2015)
Location	United States	United States	Multi-centre, multinational	England
Average number of Patients enrolled per month/centre	7	0.7	0.5	31.5
Lactate screening	None	Required	Required	Required
Existing sepsis protocols (SSC 2004, 2008, and 2012)	No	Yes, (SSC and individual centres)	Yes	
(SSC and national standards)	No			
Care provided (blinded)	ED unblinded			
ICU was blinded	ED/ICU unblinded	ED/ICU unblinded	ED/ICU unblinded	

Table 1 Study Comparison
ARisE, Australasian Resuscitation in sepsis Evaluation; ED, emergency department; EGDT, early goal-directed therapy; ICU, intensive care unit; ProCEss, Protocolized Care for Early septic shock; SSC, surviving sepsis campaign

	EGDT EGDT	Control	ARISE EGDT	PBST	UC	ARISE EGDT	UC	ProMISe EGDT	UC
Fluids prior ENR, mL			2,254	2,226	2,083				
Total fluids 0-72 hours mL			7,720	8,175	6,663	6,906	6,672	5,153	5,194
VP at enrolment, %			19.1	16.8	15.1	21			
VP 0-72 hours, %	36.8	51.3	27.3	24.0	22.4			681	608
Any inotrope, %	15.4	9.2	9.3	2.5	2.9			220	63
PRBC 0-6 hours, %	64.1	18.5	14.4	8.3	7.5	13.6	7.0	55	24
Any PRBC, %	68.4	44.5	9.3	2.5	2.9			131	74

Table 2 Interventions
ARISE, Australasian Resuscitation in sepsis Evaluation; EGDt, early goal-directed therapy; PBST, Protocol-Based standard therapy; PRBC, Packed Red Blood Cell; ProCEss, Protocolized Care for Early septic shock; UC, Usual Care; VP, vasopressor

	EGDT EGDT	Control	ProCESS EGDT	PBST	UC	ARISE EGDT	UC	ProMISe EGDT	UC
Predicted mortality based on APACHE II, %	40.3	36.9	38.2	37.5	37.9	21.0	21.0	32.2	29.1
Observed hospital mortality, %	30.5	46.4	21.0	18.2	18.9	14.5	15.7	25.6	24.6
60-day mortality, %	44.3	56.9	21.0	18.2	18.9				
90-day mortality, %			31.9	30.8	33.7	18.6	18.8	29.5	29.2
Duration hospital stay, days	13.2	13.0	11.1	12.3	11.3	8.2	8.5	9	9

Table 3. Outcomes
APACHE ii, Acute Physiology and Chronic Health Evaluation ii; ARISE, Australasian Resuscitation in Sepsis Evaluation; EGDT, early goal-directed therapy; PBST, Protocol-Based Standard Therapy; ProCEss, Protocolized Care for Early septic shock; UC, Usual Care

Myocardial Dysfunction

Suspicion of myocardial dysfunction should be raised in patients with persistently low ScvO2, elevated CVP and lactate level. This can be present in up to 15% of patients of patients in septic shock (Jozwiak et al. 2011). Bedside ultrasound may demonstrate depressed ejection fraction and decreased cardiac motility. Dobutamine is the first-line inotropic therapy due to its ability to increase cardiac output by increasing cardiac contractility and heart rate. While its use in sepsis has not been shown to improve mortality, a trial of dobutamine up to 20µg/kg/min carries a 1C recommendation by the Surviving Sepsis Campaign guidelines.

Decreasing Systemic Oxygen Demands

Increased metabolic demands, which cannot be met by increasing systemic oxygen delivery, can contribute to ongoing tissue hypoxia. Fever and increased work of breathing can account for up to 40% of oxygen consumption in sepsis and animal studies have shown mechanical

ventilation to mitigate the early effects of sepsis on haemodynamics (Correa et al. 2012; Manthous et al. 1995; Beisel 1980). Initial mechanical ventilation should be approached with caution as it can decrease venous return, and the medications used for rapid sequence intubation are associated with blunting of the sympathetic drive and arterial and venous dilation. If aggressive fluid resuscitation has yet to be undertaken, the patient can become rapidly hypotensive following intubation. When these precautions are considered and mitigated, early paralysis in patients with acute lung injury has been associated with improved outcomes.

Conclusion

A recent trilogy of studies (PROCESS, ARISE and ProMISe) sought to examine EGDT as a haemodynamic optimisation study, particularly the need for CVP and ScvO2 monitoring during resuscitation (see Tables 1-3). These studies provided early diagnosis, risk stratification (elevated serum lactate or hypotension), assessment of haemodynamic response after a fluid challenge, antibiotics, source control and early ICU admission to all groups with unblinded care in all treatment groups. This trilogy found no difference between EGDT and usual care as provided in these trials. Because of providing many components of EGDT in all treatment groups, mortality from sepsis has been reported at all time lows by all of these trials. The question remains whether an invasive or noninvasive method (with or without CVP) confers improved mortality. It must be remembered that EGDT provided no harm consistent with proven benefit in over 45 publications comprising over 40,000 patients with equal mortality benefit as the original trial (Wira 2014; Jones 2008; Barochia 2010; Wang 2012; Gu 2014). While these controversies continue to be discussed, we do know that patients with sepsis need early intervention and benefit from parameters to measure response to resuscitation.

For full references, please email **editorial@icumanagement.org**, visit **www.icu-management.org** or use the **article QR code**.

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