Goal-directed management of shock in children

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Summary

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Shock is a physiologic state characterised by a significant, systemic reduction in tissue perfusion, resulting in decreased tissue oxygen delivery. Although the effects of inadequate tissue perfusion are initially reversible, prolonged oxygen deprivation leads to generalised cellular hypoxia and derangement of critical biochemical processes. These abnormalities rapidly become irreversible and result sequentially in cell death, end-organ damage, failure of multiple organ systems, and death. The shock syndrome is characterised by a continuum of physiologic stages and may progress through three stages if not successfully treated, culminating in end-organ damage, irreversible shock, and death. The challenge for the clinician is to recognise children in shock early (before they develop hypotension), when they are more likely to respond favourably to treatment. Although the cause of shock may not be initially apparent, treatment must begin immediately. To assist with this early recognition, a systematic approach to the evaluation of children with evidence of poor perfusion typically identifies features of the history, physical examination, and ancillary studies that suggest the underlying condition. The paediatric assessment triangle (PAT) provides this systematic approach and rapidly provides a quick evaluation of appearance, breathing, and circulation for acutely ill or injured children that should identify conditions that require immediate intervention. To direct rapid and appropriate treatment, Early goal directed therapy was developed to provide an efficient and effective means of immediate intervention. Early goal directed therapy (EGDT) for shock refers to an aggressive systematic approach to resuscitation involving a series of controlled manipulations of physiologic parameters. The goal is to carry out appropriate treatment according to the algorithm within the first hour of presentation to hospital. This protocol has been used with success in the adult population for whom it was originally designed. Evidence of EGDT effectiveness in the paediatric population has grown along with it's steadily growing implementation.

Key words: Paediatric, Shock, Early goal directed therapy.

Physiology of shock in children

Shock is a physiologic state characterised by a significant, systemic reduction in tissue perfusion, resulting in decreased tissue oxygen delivery (Pomerantz & Roback 2015). Although the effects of inadequate tissue perfusion are initially reversible, prolonged oxygen deprivation leads to generalised cellular hypoxia and derangement of critical biochemical processes, including (Barber & Shires 1996; Kristensen 1994):

- Cell membrane ion pump dysfunction
- Intracellular edema
- Leakage of intracellular contents into the extracellular space
- Inadequate regulation of intracellular pH

This results in impaired vital organ function causing consequences such a depressed mental status and low urine output (Waltzman 2015). Hypo perfusion and it's myriad of effects initiate inflammatory events (such as the activation of neutrophils and release of cytokines) that disrupt the microcirculation and contribute to tissue injury. Adrenergic stress responses that are activated to compensate for decreased tissue perfusion and increased metabolic demand include the following: Blood flow to vital organs is preserved through stimulation of the heart (tachycardia and increased contractility) by the sympathetic nervous system and increased peripheral vasoconstriction (increased systemic vascular resistance and venous tone) mediated by the sympathetic nervous and renin-angiotensin systems.. Hormones such as catecholamines, corticosteroids, and glucagon initiate increased liver glycolysis and lipolysis to maintain cell energy sources, causing an increase in lactic acid production. The accumulation of lactic also occurs as cells eventually switch to anaerobic metabolism to generate energy. The effect of this accumulation is metabolic acidosis, which further interferes with cell and organ function (Waltzman 2015).

These abnormalities rapidly become irreversible and result sequentially in cell death, end-organ damage, failure of multiple organ systems, and death (Chameides et al. 2011; Tobin & Wentzel 1996). Mortality from shock is less among children than adults. For children with severe sepsis, mortality is about 10 percent, in comparison to 35 to 40 percent within one month of the onset of septic shock for adults (Watson et al. 2003; Bone 1992). Nevertheless, outcomes for children with shock (in terms of morbidity and cost) are significant.

Furthermore, unique physiologic responses to poor perfusion among children make it a challenge for clinicians to recognise shock early (before hypotension develops), when responses to treatment are more favourable (Pomerantz & Roback 2015).

Parameters that determine adequate oxygen delivery to tissues include blood flow to tissues (cardiac output), the regional balance between blood flow and metabolic demand, and the oxygen content of blood (haemoglobin concentration and percentage of haemoglobin saturated with oxygen) (Chameides et al. 2011). Physiologic variables that the body can manipulate to compensate for compromised perfusion include (Pomerantz & Roback 2015):

- Cardiac output (volume of blood flow per unit of time) is the product of stroke volume times heart rate. Hence, tachycardia is a common sign of decreased perfusion and early shock. Infants have relatively fixed stroke volumes and are particularly dependent upon heart rate to increase cardiac output.
- Stroke volume is determined by preload, cardiac contractility, and afterload. Compensatory mechanisms that improve stroke volume include increased venous smooth muscle tone (improves preload by shunting blood to the heart) and increased cardiac contractility (resulting in more complete emptying of the ventricles).
- Increased systemic vascular resistance (vasoconstriction) maintains perfusion pressure (measured as blood pressure) despite decreased cardiac output. In addition, blood is shunted away from peripheral structures (including skin, muscle, kidneys, and splanchnic organs) to the heart and central nervous system. As a result, children with compensated shock typically have normal blood pressures, despite signs of poor perfusion (such as decreased peripheral pulses and tachycardia).

While decreased perfusion directly reflects decreased cardiac output, the increased cardiac output observed in hyperdynamic shock states also is associated with decreased effective tissue perfusion (Chittock & Russell 1996). This decreased effective perfusion derives from a complex interaction of numerous humoral and microcirculatory processes resulting in patchy, uneven local regional blood flow and a derangement of cellular metabolic processes (Hinshaw 1996).

The shock syndrome is characterised by a continuum of physiologic stages beginning with an initial inciting event that causes a systemic disturbance in tissue perfusion. Subsequently,

shock may progress through three stages if not successfully treated, culminating in end-organ damage, irreversible shock, and death (Pomerantz & Roback 2015):

1. Compensated shock- The body's homeostatic mechanisms rapidly compensate for diminished perfusion and systolic blood pressure is maintained within the normal range (Chameides et al. 2011). Heart rate is initially increased. Signs of peripheral vasoconstriction (such as cool skin, decreased peripheral pulses, and oliguria) can be observed as perfusion becomes further compromised.

2. Hypotensive shock- During this stage, compensatory mechanisms are overwhelmed. Signs and symptoms of organ dysfunction (such as altered mental status as the result of poor brain perfusion) appear. Systolic blood pressure falls and once hypotension develops, the child's condition usually deteriorates rapidly to cardiovascular collapse. Although hypotension is generally a late finding among children with shock, those with early distributive shock (as with sepsis) may have hypotension because of decreased systemic vascular resistance (SVR). Vital organ perfusion is initially maintained by increased cardiac output.

3. Irreversible shock- During this stage, progressive end-organ dysfunction leads to irreversible organ damage and death. The process is often irreversible, despite resuscitative efforts.

Classification of shock

Four broad mechanisms of shock are recognised: 1. hypovolemic, 2. distributive, 3. cardiogenic, and 4. obstructive. For any given situation, the classification can be mixed. Patients with distributive shock, in particular, often have multiple physiologic abnormalities. As an example, children with distributive shock from sepsis may also have volume loss (from vomiting, diarrhoea, poor intake, or increased insensible fluid loss from tachypnea and fever) and myocardial depression from the effect of inflammatory mediators released in response to infection (Pomerantz & Roback 2015).

1. Hypovolemic shock, particularly from gastroenteritis, is the most common cause of paediatric shock worldwide (WHO 2012). The hypovolemic state results from decreased preload from extravascular fluid loss (such as with diarrhoea or osmotic diuresis) or

intravascular fluid loss (as with capillary leak or haemorrhage). Because preload is one of the determinants of stroke volume, cardiac output falls when preload drops.

2. Distributive or vasodilatory shock results from a decrease in SVR, with abnormal distribution of blood flow within the microcirculation and inadequate tissue perfusion. It can lead to functional hypovolemia with decreased preload (Chittock & Russel 1996). Distributive shock generally is associated with a normal or increased cardiac output. Systemic vascular resistance (SVR) may be low, producing increased blood flow to skin and a wide pulse pressure (warm shock) or SVR may be increased, in which case, blood flow to skin is decreased and the pulse pressure is narrow (cold shock) (Waltzman 2015). The most common aetiology of this type of shock among children is sepsis. Sepsis is a clinical syndrome that complicates severe infection and is characterised by the systemic inflammatory response syndrome, immune dysregulation, microcirculatory derangements, and end-organ dysfunction. In this syndrome, tissues remote from the original insult display the cardinal signs of inflammation, including vasodilation, increased microvascular permeability, and leukocyte accumulation (Pomerantz & Weiss 2015). The occurrence of paediatric severe sepsis has been steadily rising since the mid-1990's and now accounts for 4.4 percent of admissions to children's hospitals and 7 percent of patients treated in paediatric intensive care units in the United States (Hartman et al. 2013; Balamuth et al. 2014). Other causes of distributive shock are anaphylaxis and neurogenic shock.

3. Cardiogenic shock results from pump failure, manifested physiologically as decreased systolic function and depressed cardiac output (Rodgers 1995). Cardiogenic shock is uncommon among children, as compared with adults, among whom ischemic heart disease is the major cause. The mechanisms of cardiogenic shock are diverse and can be divided into two general categories: cardiomyopathies and arrhythmias (Witte & Blumer 1987; Bengur & Melons 1998).

4. Obstructive shock and impaired cardiac output result when blood flow is physically obstructed. Acquired causes of obstructive shock include cardiac tamponade, tension pneumothorax and massive pulmonary embolism. Infants with ductal-dependent congenital heart lesions, such as coarctation of the aorta and hypoplastic left ventricle syndrome, may present in shock when the ductus arteriosus closes during the first few weeks of life (Chameides et al. 2011).

Although the clinical presentation of shock is variable, several features are common to the four types of shock. These include tachycardia and signs of compromised organ perfusion. Children often present before hypotension develops (Pomerantz & Roback 2015).

1. Although tachycardia is an important early indicator of shock, it is a nonspecific finding. Many common conditions in children such as fever, pain, and anxiety can cause tachycardia without circulatory compromise. A normal heart rate with signs of compensated shock can occur with spinal cord injury and bradycardia can occur as the result of hypoxia or some ingestions (such as beta blockers).

2. Skin changes- Regulatory processes compensate for decreased effective tissue perfusion. Potent vasoconstrictive mechanisms redirect blood from the peripheral, splanchnic, and renal vessels to maintain coronary and cerebral perfusion. As a result, the skin is typically cool, clammy, pale, or mottled. Notable exceptions are the flushed, hyperaemic skin of early distributive shock and the peripheral vasodilation of terminal shock states associated with failure of mechanisms that maintain increased peripheral vascular resistance (irreversible shock).

3. Impaired mental status- Children with impaired cerebral perfusion may be initially listless or agitated and not interacting with those around them. Mental status typically deteriorates to obtundation and coma as the shock state progresses.

4. Oliguria with decreased glomerular filtration rate results from the shunting of renal blood flow to other vital organs and the fall in intraglomerular pressure, which normally drives glomerular filtration.

5. Lactic acidosis-Two factors contribute to this abnormality: increased lactic acid production caused by inadequate delivery of oxygen and decreased clearance of lactate by the liver, kidneys, and skeletal muscle (Levraut et al. 1998). The early stages of sepsis often are associated with a respiratory alkalosis caused by primary hyperventilation (Simmons et al. 1960).

6. Hypotension is typically a late finding among children in shock. Compensatory vasoconstriction is often so pronounced that systemic blood pressure can be maintained within the normal range, despite significant circulatory compromise. In this situation, the main clinical manifestations of shock are tachycardia and signs of organ hypoperfusion.

For children, hypotension is defined as a systolic blood pressure that is less than the fifth percentile of normal for age (Chameides et al. 2011):

• Less than 60 mmHg in term neonates (0 to 28 days)

• Less than 70 mmHg in infants (1 month to 12 months)

• Less than 70 mmHg + (2 x age in years) in children 1 to 10 years

• Less than 90 mmHg in children 10 years of age or older

Evaluation of shock in children

Children can compensate for circulatory dysfunction (primarily by increasing heart rate, systemic vascular resistance, and venous tone) and maintain normal blood pressures despite significantly compromised tissue perfusion (Waltzman 2015). Consequently, hypotension is a very late and ominous finding (Schwaitzberg et al. 1988). The challenge for the clinician is to recognise children in shock early (before they develop hypotension), when they are more likely to respond favourably to treatment. Although the cause of shock may not be initially apparent, treatment must begin immediately. A systematic approach to the evaluation of children with evidence of poor perfusion typically identifies features of the history, physical examination, and ancillary studies that suggest the underlying condition. The goals of the initial evaluation of shock in children include (Waltzman 2015):

- Immediate identification of life-threatening conditions (e.g. tension pneumothorax, hemothorax, cardiac tamponade, or pulmonary embolism)
- Rapid recognition of circulatory compromise
- Early classification of the type and cause of shock

To assist with this initial evaluation, the paediatric assessment triangle (PAT) rapidly provides a quick evaluation of appearance, breathing, and circulation for acutely ill or injured children that should identify conditions that require immediate intervention. Features of the PAT that are specific for the evaluation of shock include:

Appearance- Significant changes in appearance (such as poor tone, unfocused gaze, or weak cry) may be indicators of decreased cerebral perfusion. Subtle differences in appearance (such as decreased responsiveness to to painful procedures) may also be important indicators of shock.

Breathing- A child with depressed mental status as the result of shock may not be able to maintain a patent airway. Tachypnea without respiratory distress can develop in response to metabolic acidosis. Children with cardiogenic shock typically have some increased work of breathing in addition to tachypnea (Waltzman 2015).

Circulation- Poor perfusion can often be identified rapidly, before a blood pressure measurement is taken. Features of circulation that should be quickly evaluated include (Waltzman 2015):

- Quality of central and peripheral pulses – Decreased intensity of distal pulses in comparison to central pulses suggests peripheral vasoconstriction and compensated shock.
- Bounding pulses may be present in patients with distributive ("warm") shock.
- Skin temperature – Skin may be mottled or cool in children with compensated shock, but this finding can also be influenced by environmental temperature.
- Capillary refill – Capillary refill greater than two seconds suggests shock. The usefulness of capillary refill is limited by inter observer variability and by the effect of environmental temperature. Flash capillary refill (<1 second) may be present in patients with distributive ("warm") shock.
- Heart rate – Tachycardia is frequently present although a normal or low heart rate with signs of compensated or hypotensive shock can occur with cervical or high thoracic spinal cord injury.

History- A history of fluid loss (due to gastroenteritis, diabetic ketoacidosis, or a gastrointestinal bleed) is consistent with hypovolemic shock. Children who have been injured may have hypovolemic shock from haemorrhage (e.g. solid organ injury from blunt abdominal trauma), obstructive shock (e.g. tension pneumothorax or cardiac tamponade), and/or neurogenic shock (e.g. spinal cord injury). Fever and/or immunocompromise (due to chemotherapy, sickle cell disease, or inherited immunodeficiencies) may indicate septic shock. A history of exposure to an allergen (e.g. a bee sting or food) suggests anaphylactic shock. Adrenal crisis must be considered in a patient at risk for adrenal insufficiency (e.g. patients receiving chronic steroid therapy, hypopituitarism, neonates with congenital adrenal disease, or sepsis) (Waltzman 2015).

Physical examination- The characteristic changes in respiratory rate, heart rate and blood pressure have already been mentioned. Additional features that suggest the aetiology of the shock include the following (Waltzman 2015):

Stridor, wheezing, or abnormal breath sounds- Children with stridor or wheezing may have anaphylaxis. Those with crackles may have a pneumonia (septic shock) or heart failure (cardiogenic shock). Those with asymmetric breath sounds may have a tension pneumothorax. Airway obstruction from other causes (such as foreign body aspiration or status asthmaticus) may lead to cardiovascular collapse from hypoxemia.

Distended neck veins- Distended neck veins suggest an abnormality of cardiac contractility with heart failure, or obstruction to venous return caused by cardiac tamponade or tension pneumo/hemothorax.

Abnormal heart sounds- Cardiogenic shock is suggested by cardiac murmurs or a gallop rhythm. Muffled heart tones suggest pericardial fluid and, when accompanied by pulsus paradoxus identifies cardiac tamponade.

Pulse differential- Decreased pulses and/or blood pressure in the lower extremities when compared to the upper extremities suggests coarctation of the aorta or other structural heart disease.

Hepatomegaly- Hepatic congestion and resulting hepatomegaly can be seen with heart failure.

Abnormal abdominal findings- Abdominal distention, masses, or tenderness is consistent with urgent conditions such as bowel obstruction, perforation, or peritonitis.

Abnormal skin findings – Urticaria or facial oedema suggests anaphylaxis but is not a consistent finding in severe reactions. Purpura can be seen with septic shock.

Ancillary studies may be useful for successfully treating shock, identifying the aetiology, and monitoring response to treatment. Ancillary studies should be simultaneously obtained with rapid assessment and treatment based upon the most likely(discussed in detail in the following section).

Management of shock using early goal directed therapy

Early goal directed therapy (EGDT) for shock refers to an aggressive systematic approach to resuscitation involving a series of controlled manipulations of physiologic parameters. These physiologic indicators of perfusion and vital organ function guide the therapeutic interventions and the aim is to improve, maintain or correct organic functions at a cellular level as well as maintaining metabolic and endocrine homeostasis within the first six hours (Arnal & Stein 2003; Waltzman 2015). Initial interventions are oriented toward correcting tissue hypoxia, manipulating cardiac preload, afterload and contractility to balance oxygen delivery with oxygen demand (Arnal & Stein 2003). This method of resuscitation when applied early enough (within 6 hours from hospital admission) has been shown to improve outcome and has been strongly promoted for children with septic shock (Arnal & Stein 2003) although it can generally be applied to most patients presenting with shock (Waltzman 2015). Once initial stabilisation of the patient has been managed, the exact aetiology of shock must be diagnosed to best direct subsequent therapy (Waltzman 2015).

The first priority is to resuscitate the patient to specific clinical goals (Carcillo et al. 2007). The following are the basic physiologic indicators and target goals (Carcillo & Fields 2002; Brierley et al. 2009) (see Figure 2 for more detail):

- Blood pressure (systolic pressure at least fifth percentile for age: 60 mmHg <1 month of age, 70 mmHg + [2 x age in years] in children 1 month to 10 years of age, 90 mmHg in children 10 years of age or older)
- Quality of central and peripheral pulses (strong, distal pulses equal to central pulses)
- Skin perfusion (warm, with capillary refill <2 seconds)
- Mental status (normal mental status)
- Urine output (≥1 mL/kg per hour, once effective circulating volume is restored)
- Lactate (<4mmol/L or >10% decrease per hour until normal)
- Central venous oxygen saturation ($Scv0_2$), (>70%).

(The distal pulse quality, temperature and capillary refill reflect systemic vascular tone and cardiac output. Normal capillary refill and toe temperature indicated a cardiac index of >2L/min/m^2) (Carcillo et al. 2007).

Patients should be rapidly assessed for the presence of shock and the initial management for hypovolemic, distributive and cardiogenic shock should be focused on fluid resuscitation with the appropriate solutions. Evaluation of physiologic indicators should be carried out before and after each intervention step. Once physiologic goals have been achieved, continuous supportive treatment and monitoring is required and normal blood pressure must be maintained. For children with compensated shock and normal blood pressures, therapeutic endpoints based upon noninvasive indicators are reasonable targets (Waltzman 2015).

The following algorithm (Figure 1) for EGDT demonstrates the time line within which physicians should carry out the interventions. Although not always attainable, the time sequence provides a point of reference which highlights the urgency of the situation.

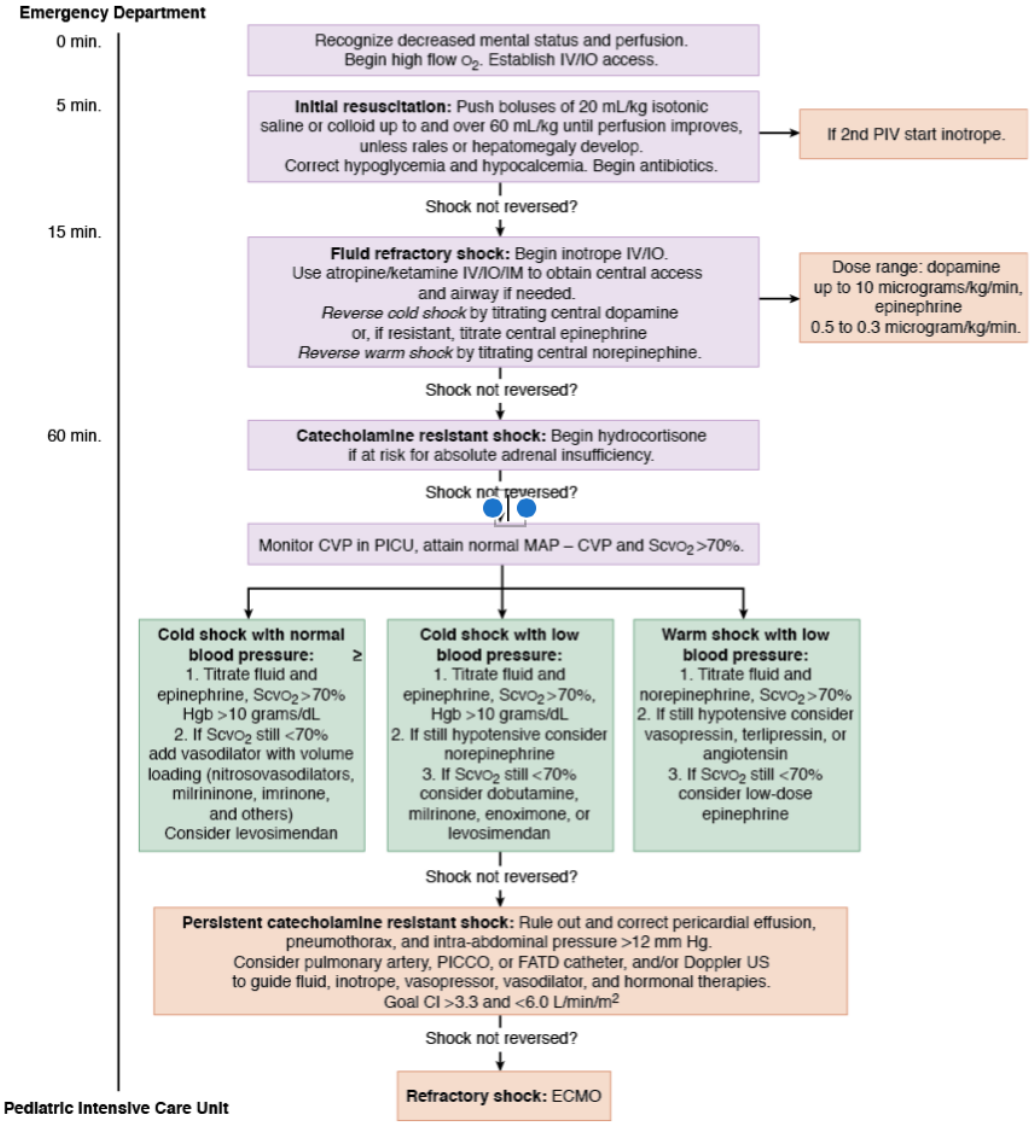

Figure 1. Early goal directed therapy algorithm according to: Tintinalli et al. 2004

Physiologic Parameter	*Therapeutic Goal*	*Monitoring Method*	*Manipulation*
Tissue perfusion	• Capillary refill <2 sec • Mean arterial pressure 65–70 mmHg • Urine output >0.5 ml/kg/hr • CVP 8–12 mm Hg	• Capillary refill • Mean arterial pressure • Urine output • CVP	• Fluids (crystalloids, colloids): 20 ml/kg bolus. 40–60 ml/kg in 1st hr. • Sympathomimetics: Dopamine (1st-line), norepinephrine or epinephrine (2nd-line) • Vasodilators: Nitroprusside
Oxygenation	• O_2 sat >93% • Central venous O_2 sat>70% • Hb within normal range for age • Hct 30% • O_2 extraction 0.3–0.6. • Serum lactate <2 mmol/L	• O_2 saturation • Central Venous O_2 Sat • Hemoglobin concentration • Hematocrit • Arterial blood gases • O_2 extraction: $(CaO_2\text{-}CvO_2)/CaO_2$. • Serum lactate	• FIO_2 • PEEP • Mean arterial pressure • Transfusion (blood, PRBC) if Hb <10 mg/dl
Urine output and renal perfusion	• Urine output >0.5 ml/kg/hr	• Urine output • Creatinine clearance • BUN	• Continuous renal replacement therapy: CVVH/D at 10% fluid overload or acute renal failure • Dialysis
Metabolic and Nutritional support	• Glucose 80–110 mg/dl • ICa^{++}: 1.14–1.29 • Positive nitrogen balance	• Serum glucose • Serum ICa^{++} • Healing of wounds and overall status • Weight • Albumin-prealbumin, total protein, Albumin/globulin ratio • Indirect calorimetry	• Dextrose • Insulin • ICa^{++} • Enteral feeding • TPN • Micronutrients: vitamins (vit K), mineral
Adrenal support	• Prevention of adrenal insufficiency and refractory hypotension	• Cortisol level • Blood pressure • Therapeutic trial	• Hydrocortisone

CVP: central venous pressure, CVVHD: continuous venovenous hemofiltration/dyalisis, PEEP: positive end expiratory pressure, PRBC: packed red blood cells.[1,10-19]

Figure 2. Therapeutic target goals according to: Luisa E. Arnal, Fernando Stein (2003)

Within the initial 0-15 minutes of therapy:

Airway and Breathing- 100% supplemental oxygen should be delivered to optimise blood oxygen content with continuous pulse oximetry ($Sp0_2$). Once target perfusion has been restored, supplemental oxygen should be titrated to avoid hyperoxia and free radical associated adverse effects (lung injury etc) (Asfar et al. 2009). Children with shock will frequently require rapid sequence intubation (RSI). This allows airway protection, ventilation assistance and reduced work of breathing which can prevent diversion of valuable cardiac output to the muscles of respiration (Weiss & Pomerantz 2015). When performing RSI in children, hemodynamic instability must be addressed prior to or during intubation. Ketamine, if not contraindicated, is the preferred sedating agent (Etomidate should not be used as it inhibits cortisol formation) (Weiss & Pomerantz 2015)

Monitoring and Evaluation- Frequent monitoring of physiologic parameters and the appropriate adjustments of therapeutic adjustments are the core of EGDT. This therefore requires continuous hemodynamic monitoring and end organ perfusion assessment (brain, kidneys, skin) (Waltzman 2015). During the initial stage of shock, many parameters can be monitored non invasively and if the child responds well, invasive monitoring can often be avoided (Carcillo & Fields 2002). Continuous measurement of heart rate and pulse oximetry is necessary with frequent blood pressure measurements. In addition to these parameters, the following should be assessed before and after each fluid bolus:

- Quality of central and peripheral pulses
- Skin perfusion (indicated by temperature and capillary refill)
- Mental status
- Auscultation of lung and heart sounds
- Palpation of liver edge (to identify hepatomegaly as a sign of heart failure)
- A urinary catheter should be placed to monitor urine output

The quality of central and peripheral pulses, skin perfusion, mental status and urine output have all been shown to be appropriate signs of the response to therapy (Waltzman 2015).

More aggressive and invasive monitoring may be necessary for children who do not initially improve with fluid resuscitation.

Other diagnostic studies should be obtained as indicated by clinical assessment. These are discussed below.

Arterial or venous blood gas- patients frequently have inadequate tissue perfusion with lactic acidosis. Hypoxemia from bronchopneumonia or pulmonary oedema may also occur (Weiss & Pomerantz 2015).

Complete blood count with differential (including platelet count)- Age specific leukocytosis or leukopenia are a criteria for establishing a paediatric SIRS diagnosis. Neutrophilia, neutropenia or thrombocytopenia may indicate acute infection.

Blood Glucose- Children with shock are at risk of hypoglycaemia and so rapid measurement of blood glucose should be obtained followed by rapid treatment of hypoglycaemia using an intravenous infusion of dextrose. Once the initial hypoglycaemia has been corrected, a continuous infusion of dextrose should be administered to maintain blood glucose between 70-150 mg/dL (3.89-8.33 mmol/L). In normoglycemia children, a continuous maintenance infusion of 10% dextrose is suitable as suggested by the American College of Critical Care Medicine (Brierley et al. 2009).

Calcium and electrolytes-Children with an ionised calcium measurement <1.1 mmol/L (4.8mg/dL) or symptomatic hypocalcemia (positive Chvostek/Trousseau signs, seizures, prolonged QT interval or cardiac arrhythmias) should be given 50-100 mg/kg (0.5-1mL/kg) of 10% calcium gluconate solution, up to 2g (20ml), by slow intravenous or intraosseous infusion over 5 minutes. Calcium should be administered in a larger vein or a central line. Sodium Bicarbonate should not be given into the same cannula without prior flushing because of potential precipitation (Weiss & Pomerantz 2015). All patients receiving calcium infusions must receive continuous cardiac monitoring. Other electrolyte abnormalities (hyponatermia, hyperkalemia, hypokalemia and hypophosphatemia) may be present especially when other conditions are present such as syndrome of inappropriate anti-diuretic hormone secretion, gastroenteritis and capillary leak (Waltzman 2015).

Blood Lactate-This can be measured using an arterial puncture or from an indwelling vascular cannula. Levels above 3.5-4mmol/L can indicate the presence and severity of shock

at presentation (Carcillo & Fields 2002). The evidence for this parameter is limited in children however studies on adults in shock have shown that a reduction in blood lactate levels is associated with improved survival (Myburgh & Finfer 2013; Perez et al. 2010; Arnold et al. 2009). One study conducted on children with SIRS did show that initial blood lactate levels over 4mmol/L were associated with rapid progression to organ dysfunction (Scott et al. 2012). An alternative biochemical goal also addressing acidosis is the anion gap. This can be used to assess the presence of anaerobic metabolism. The goal is to maintain the anion gap at less than 16mmol/L. The benefit of using the anion gap is that even if the patient has received bicarbonate therapy, the acidosis might be masked but not the anion gap. Non anion gap acidosis can be caused by excess chloride from saline resuscitation (Carcillo et al. 2007).

Blood urea nitrogen (BUN) and serum creatinine- Elevation in BUN can indicate dehydration and an elevated creatinine level could be due to prerenal azotemia. These parameters allow for renal monitoring and serum creatinine >2 times the upper limit of normal for age or a two-fold increase in baseline creatinine indicate renal dysfunction (Weiss & Pomerantz 2015).

Serum total bilirubin and alanine aminotransferase (ALT)- Total bilirubin >4mg/dL (not applicable to newborns) or ALT >2 times upper limit of normal for age indicate liver dysfunction.

Prothrombin time (PT), partial thromboplastin time (aPTT), internal normalised ratio (INR), fibrinogen and D-dimer- Consumptive coagulopathy and disseminated intravascular coagulopathy are severe complications of shock and can be identified when PT, aPTT, INR or D-dimer are elevated along with decreased fibrinogen.

Blood culture- In the setting of suspected septic shock, blood cultures should always be obtained, preferably before empirical antibiotic therapy is initiated.

Urinalysis and urine culture- The presence of bacteria, nitrites or pyuria suggests a urinary tract infection and can indicate the source of infection in septic shock. Urine cultures, just as blood cultures, should ideally be obtained before empirical antibiotic therapy is commenced.

Anaphylaxis-Any child with signs of anaphylaxis should receive intramuscular epinephrine, diphenhydramine and hydrocortisone.

IV access/Fluid therapy-Two vascular or intraosseous access sites should be established as rapidly as possible. Initial fluid resuscitation should be started with isotonic crystalloid infusions. A 20mL/kg infusion over 5 minutes should be given to hypotensive children without signs of cardiogenic or obstructive shock. Patients with compensated shock should still receive the same rapid infusion over 5-20 minutes as long as there are not signs of cardiogenic or obstructive shock, diabetic ketoacidosis (DKA) or other conditions that may worsen with fluid administration (Waltzman 2015). In the case of cardiogenic shock, fluid must be administered cautiously and at a lower volume (5-10ml/kg over 10-20 minutes). (Waltzman 2015). The presence of DKA requires careful fluid resuscitation with one bolus of 10ml/kg over one hour. After initiating the initial fluid bolus in any child with shock, the following physiologic indicators should be evaluated and then repeatedly checked before and after each subsequent infusion (Waltzman 2015):

- Blood pressure (systolic pressure at least fifth percentile for age: 60 mmHg <1 month of age, 70 mmHg + [2 x age in years] in children 1 month to 10 years of age, 90 mmHg in children 10 years of age or older)
- Quality of central and peripheral pulses (strong, distal pulses equal to central pulses)
- Skin perfusion (warm, with capillary refill <2 seconds)
- Mental status (normal mental status)
- Urine output (≥1 mL/kg per hour, once effective circulating volume is restored)

Within 15-30 minutes of presentation:

If shock has not been reversed or responded to therapy, central access and airway support should be obtained if not already done.

IV fluids- If there has not been an improvement, patients should continue to receive isotonic crystalloid in 20ml/kg boluses to a total of 60ml/kg over the first 30 minutes of treatment (excluding those with obstructive shock, cardiogenic shock or DKA) (Waltzman 2015). Testing for signs of fluid overload (decreased oxygenations, rales, gallop rhythm, tachypnea, wet cough and hepatomegaly) must be done before and after each bolus (Carcillo et al. 2007). Presence of these signs is usually an indication to stop fluid resuscitation and initiate inotrope therapy.

Pharmacological agents-Vasoactive drug therapy is suggested for children with cardiogenic or septic shock who have not responded to isotonic fluid resuscitation (up to 60ml/kg or more). At this point, arterial pressure monitoring is recommended (placement of intrarterial catheter). If cold shock has been identified, this can be treated with central dopamine or if resistant, central epinephrine. Warm shock should be reversed with norepinephrine (Waltzman 2015).

Antibiotics-In the case of septic shock, appropriate antibiotics as determined by the institution should be administered.

Within 30-60 minutes:

Children who have not improved by this point must be reevaluated for other causes of shock. The amount of fluid loss may have been underestimated or there may be significant unrecognised fluid loss. Children with hypovolemic shock should have their fluid losses reassessed, continued fluid replacement and potentially a switch to colloid or blood transfusion (Carcillo & Fields 2002). Unresponsive shock at this point may require the addition of corticosteroid therapy (Waltzman 2015). All patients with fluid and/or catecholamine resistant shock should at this point be in an intensive care unit and, if not already established, have invasive monitoring providing central venous pressure (CVP) and central venous oxygen saturation ($ScvO_2$). CVP provides an indication of cardiac preload and a measurement <8mmHg suggests that fluid resuscitation has been inadequate. $ScvO_2$ allows monitoring of oxygen supply and tissue oxygen consumption, both of which indicate tissue perfusion adequacy (target goal is >70%) (Carcillo & Fields 2002). $ScvO_2$ is usually measured using a catheter with the tip in the superior vena cava (Dueck et al. 2005). Although lactate clearance has been used as an alternative to $ScvO_2$ in adults, evidence for this in children is lacking. It is important to note that an $ScvO_2$ >70% in septic shock can be misleading due to hyper dynamic cardiac function, microcirculatory shunting and mitochondrial dysfunction (Velissaris et al. 2011).

The next steps carried out in the PICU can be seen in the algorithm (Figure 1) and these involve identifying the nature of the shock (cold vs warm) and the blood pressure and proceeding with the appropriate steps for treatment.

The physiology and rationale behind key components of the EGDT algorithm

Hemodynamic stability-tissue perfusion:

Heart rate is an important physiologic indicator of circulatory status. Tachycardia is often the compensatory response to poor tissue perfusion characteristic of shock and a decrease in heart rate after fluid therapy can be a valuable indicator of improved perfusion (Waltzman 2015). Returning the patient to normal heart rate and normal perfusion pressure for age are the initial hemodynamic goals and the primary purpose of fluid resuscitation . When fluid resuscitation is effective, heart rate will decrease, mean arterial pressure (MAP)-central venous pressure (CVP) will increase and the starling curve will be optimised to provide optimal cardiac output (Carcillo et al. 2002). If too much fluid is given the heart rate will increase again and MAP-CVP will decrease. As mentioned in the algorithm (figure 1), the goal is to reach a CVP of 8-12 mmHg (Arnal & Stein 2003) using bolus fluid administration with isotonic crystalloids (e.g. normal saline or Ringer's lactate) (Waltzman 2015). The use of rapid volume bolus therapy not only restores intravascular volume, it also reduces the expression of inflammation and coagulation genes (Carcillo et al. 2007). The use of colloids has not been shown to be more effective than crystalloids and is not recommended for initial fluid resuscitation (they are sometimes used for non responsive shock after crystalloid infusion) (Ngo et al. 2011; So et al. 1997; Wills et al. 2005). The shock index (heart rate/ systolic blood pressure, HR/SBP) can also be used to assess the effectiveness of fluid and inotrope therapy. With efficient fluid replacement, the heart rate as mentioned will decrease and SBP will increase resulting in a decreased shock index. In patients with superior vena cava central venous catheters, oxygen saturation can be measured with a target goal of >70%. The $AVDO_2$ can also be calculated with a goal of 3-5% (this measurement if most accurate when the central venous catheter is placed in the pulmonary artery) (Carcillo et al. 2007). There are various techniques to measure cardiac output (e.g Doppler echocardiography, Swan-Ganz catheters) or it is based on blood pressure and end organ perfusion. The goal is a cardiac index of >2L/min/m^2 in cardiogenic shock and between 3.3-6 L/min/m^2 (Carcillo et al. 2007).

Blood transfusions may be required in specific situations such as shock in the presence of anaemia. The last 20% of oxygen bound to haemoglobin cannot be extracted by mitochondria and under normal circumstances the mitochondria only use 25% of the bound

oxygen. This is why the mixed venous oxygen saturation is 75% when a healthy person has an arterial blood oxygen saturation of 100%. In a child with 10g/dL haemoglobin, only 8g/dL is available for extraction and 2.5g/dL of that is used for oxygen extraction (leaving 5.5g/dL surplus). In states of hemolysis, this surplus can be lost or the total haemoglobin level can drop below 5g/dL resulting in haemolytic shock. This is associated with an increased mortality rate. Rapid fluid administration in these situations (haemoglobin <5g/dL) will further dilute the haemoglobin concentrations, impair oxygen delivery and precipitate heart failure (Duke 2011). The same scenario occurs with hemorrhagic shock. It is during these circumstances that a blood transfusion can be life saving.

Pharmacologic therapy:

Pharmacologic agents that have effects on myocardial contractility, heart rate and the vascular tone play an important role at various stages of shock therapy. As useful as they are, many considerations must be considered before administering these drugs and inappropriate use can lead to end organ ischemia. Drugs that are typically used during the initial management of shock include dopamine, epinephrine, norepinephrine, dobutamine and phosphodiesterase enzyme inhibitors. The choice of agent depends on which physiologic parameters require manipulation and the also the aetiology of the shock (Tobias 1996).

Inotropes and Inovasopressors-

These sympathomimetic agents are indicated when cardiac output and mean arterial pressure are insufficient and the patient is suffering from inadequate organ perfusion despite fluid administration (Arnal & Stein 2003).

Dopamine is the most commonly used dose-dependent inotrope/vasopressor. It is the first ling drug for fluid refractory hypotensive shock with low systemic vascular resistance (Waltzman 2015). The effects of dopamine via different receptors are dose and age dependent. At a dose range of 3 to 10 μg/kg/min, the β_1-adrenergic receptor is stimulated, stimulating the heart but also improving renal flow. At doses of more than 10 μg/kg/min, the α_1-adrenergic receptor effect becomes predominant causing vasoconstriction and increased systemic vascular resistance (Carcillo et al. 2007). The adequate dose for a patient will depends on the hemodynamic status and therapeutic endpoints. Infants under the age of 6 months may have insensitivity to dopamine making rendering it ineffective.

If myocardial function is decreased and systemic vascular resistance increased, it is usually recommended to add dobutamine (Witte & Blumer 1987). The purpose of this inotropic agent is to increase cardiac contractility and cardiac output (Carcillo et al. 2007). Dobutamine acts as a a partial β_1-adrenergic agonist, resulting in chronotropic and inotropic effects. As with dopamine, there is an age-specific insensitivity to dobutamine in children. This insensitivity appears to be present in children younger than 2 years (Perkin et al. 1982). Another important feature of this agent is that at dosages over 10 μg/kg/min, a significant reduction in afterload can occur and occasionally hypotension. This is thought to occur because dobutamine at this dose has some some α_2 receptor effects that inhibit the release of norepinephrine from the presynaptic terminal which in turn reduces vascular tone (Carcillo et al. 2007).

If shock is refractory to dopamine and dobutamine, epinephrine (for cold shock) and norepinephrine (for warm shock) are the recommended agents (Carcillo et al. 2007). Epinephrine is a β_1-, β_2-, α_1-, and α_2-adrenergic agonist. At a lower dose (0.05 μg/kg/min) the β_S-adrenergic effect negates the α_1- adrenergic effect, producing nearly pure inotropic effects. The α_1-adrenergic effects (vasoconstriction) become more prominent as the epinephrine dose approaches and exceeds 0.3 μg/kg/min (Carcillo & Fields 2002). Patients with heart failure must be treated cautiously with epinephrine, usually in combination with a vasodilator. Norepinephrine is particularly effective for dopamine resistant shock and it acts through the β_1-, α_1-, and α_2-adrenergic receptors. Although norepinephrine always acts as an inotrope, its vasopressor effects predominate even at low dosages. This agent is most useful for maintaining adequate perfusion pressure (especially to the kidneys) in children with shock (Carcillo et al. 2007).

When considering the use of sympathomimetic agents, the dosages must be continuously titrated based on the monitored physiologic parameters. If more than 3 agents are required then it is useful to perform invasive hemodynamic monitoring as suggested by the EGDT algorithm (Arnal & Stein 2003).

Vasodilators-

These agents are indicated when a patient has low cardiac output with high vascular resistance. The first line drugs are nitroprusside and nitroglycerin. In cases of

nitrosovasodilator resistant shock, amrinone or milrinone (both phosphodiesterase enzyme inhibitors, PDEI) are indicated (Arnal & Stein 2003). The purpose of vasodilators is to reduce the pulmonary or systemic vascular resistance to allow cardiac output to increase. Nitroglycerin has somewhat selective dose-dependent effects. It is a coronary artery vasodilator at less than 1 μg/kg/min, a pulmonary vasodilator at 1 μg/kg/min, and a systemic vasodilator at 3 μg/kg/min (Carcillo et al. 2007).

Inodilators-

Amrinone and milrinone (PDEI) both improve cardiac contractility and reduce afterload and are often used when treating cardiogenic shock (Brierley 2007). The mechanism of action is the prevention of cAMP hydrolysis and when administered alone, this increase in cAMP improves contractility, diastolic relaxation and vasodilation of pulmonary and systemic vasculature. The interaction of these agents with concomitant inotropes and even vasopressors can be useful when treating shock. Norepinephrine can become a more effective inotrope while maintaining vasopressor effectiveness when administered with a type III PDEI. The β_1 receptor production of cAMP is not hydrolysed. Increased cardiac cAMP leads to improved contractility and relaxation. The α_1- and α_2-adrenergic effects remain the same because in the absence of β_2 stimulation, milrinone has a minimal effect on vasodilation compared with the norepinephrine mediated α-adrenergic vasoconstriction (Carcillo et al. 2007). The key complication when using PDEI is adjusting to the prolonged half life (hours) compared with catecholamines and nitrosovasodilators (minutes). This becomes even more important in the presence of organ failure as milrinone is eliminated by the kidneys and amrinone by the liver.

Vasopressors-

There has been renewed interest in angiotensin and vasopressin. Angiotensin has a longer half life than catecholamines and it mediates blood pressure effects through the angiotensin receptor and increased aldosterone secretion. Vasopressin not only interacts with the vasopressin receptor but also increases the release of adrenocorticotropic hormone and subsequent cortisol release. Both agents must be used with caution as they can reduce cardiac output in children with poor cardiac function (Carcillo et al. 2007).

Hydrocortisone-

Many children are treated for chronic illnesses with steroids and therefore experience pituitary adrenal axis suppression. It is also becoming more common to find central and peripheral adrenal insufficiency in the intensive care unit. Conditions such as Waterhouse-Friderichsen syndrome or reduced cytochrome P450 activity result in reduced production of aldosterone and cortisol. To make matters more complicated, adrenal insufficiency can present with low CO and high SVR or with high CO and low SVR. As highlighted in the algorithm (figure 1), any shock resistant to epinephrine or norepinephrine should raise suspicions of adrenal insufficiency and a cortisol level under 18mg/dL can aid in the diagnosis (Carcillo & Fields 2002). In this situation, hydrocortisone succinate therapy should be initiated at a dose of 50mg/kg followed by the same dose over 24 hours (Bettendorf et al. 2000). Hydrocortisone is preferred to methylprednisone or dexamethasone as it has both glucocorticoid and mineralocorticoid effects (Carcillo et al. 2007).

Antibiotic therapy

When an infection is suspected, appropriate cultures should be obtained and followed by empiric antibiotic therapy immediately. The choice of antimicrobial agents is based on the most common etiologic agent according to age, immunologic status, nosocomial versus community-acquired pathogens, microbial susceptibility patterns, tissue penetration, and toxicity. Drainage of abscesses when present should be performed (Arnal & Stein 2003).

Evidence for early goal directed therapy in children

Available observational evidence supports the use of an early goal-directed approach (including physiologic targets, fluid administration, and pharmacologic therapy) for the initial management of hypovolemic and septic shock in children. These studies, when combined with clinical experience and an understanding of the pathophysiology of shock, suggest that many children with shock benefit from early, aggressive treatment targeted to improvement in physiologic indicators that are reliable and easy to evaluate (Waltzman 2015):

An observational study (Carcillo et al. 2009) of 1422 children with signs of shock (abnormal capillary refill, tachycardia, and/or hypotension) who were transferred from a community hospital setting to a tertiary care paediatric facility found that early reversal of shock in the

community hospital and use of Paediatric Advanced Life Support/Advanced Paediatric Life Support (PALS/APLS) interventions were associated with a decrease in mortality and morbidity (permanent neurologic dysfunction) regardless of underlying aetiology (e.g. trauma, sepsis) [25]. When adjusted for severity of illness, trauma status (trauma versus no trauma), and treating facility, early reversal of shock was associated with a 57 percent reduction in mortality and functional morbidity (odds ratio [OR]: 0.4; 95% CI: 0.3-0.7). Death occurred in 16 percent (163 of 996 patients) without early shock reversal versus 5 percent (26 of 514 patients) with early shock reversal.

Institution of timely goal-directed interventions by a mobile intensive care team, including early and aggressive bolus colloid administration, endotracheal intubation and mechanical ventilation, and vasoactive therapy in conjunction with regionalisation of care for 331 children with meningococcemia in the United Kingdom was associated with a decrease in the case fatality rate from 23 to 2 percent over five years (annual reduction in the odds of death 0.41, 95% CI: 0.27-0.62) (Booy et al. 2001).

The use of goal-directed therapy has been associated with reduced mortality in children with severe sepsis [2]. As an example, in one institution, the mortality rate from purpura and severe sepsis decreased from approximately 20 to 1 percent [28]. Similarly, in the United States, death from severe sepsis was estimated as 4 percent (2 percent in healthy children and 8 percent in children with prior chronic illness) in 2003 compared with 9 percent in 1999 (Odetola et al. 2007).

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Biography:

Joseph Patten was born in Cairo, Egypt 1987. After attending the British International School in Cairo, he completed his Bachelor of Science degree in Sport and Exercise Science at the University of Bath in the United Kingdom. After realising his desire to study and practice Medicine, Joseph joined the English program for medical studies at the University of Zagreb. In the future, Joseph hopes to practice paediatric medicine.