Approach to the critically ill child with sepsis

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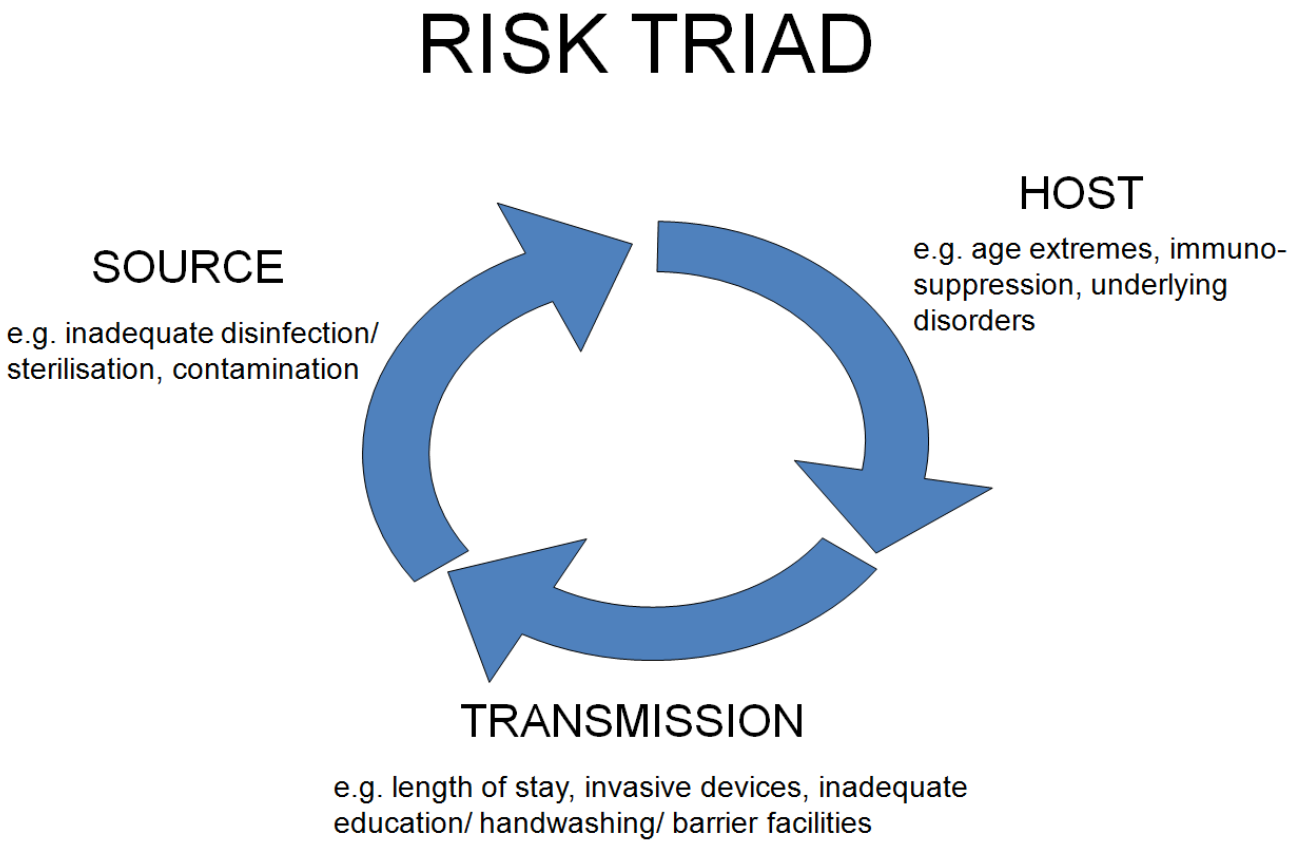
FEVER IN THE ICU

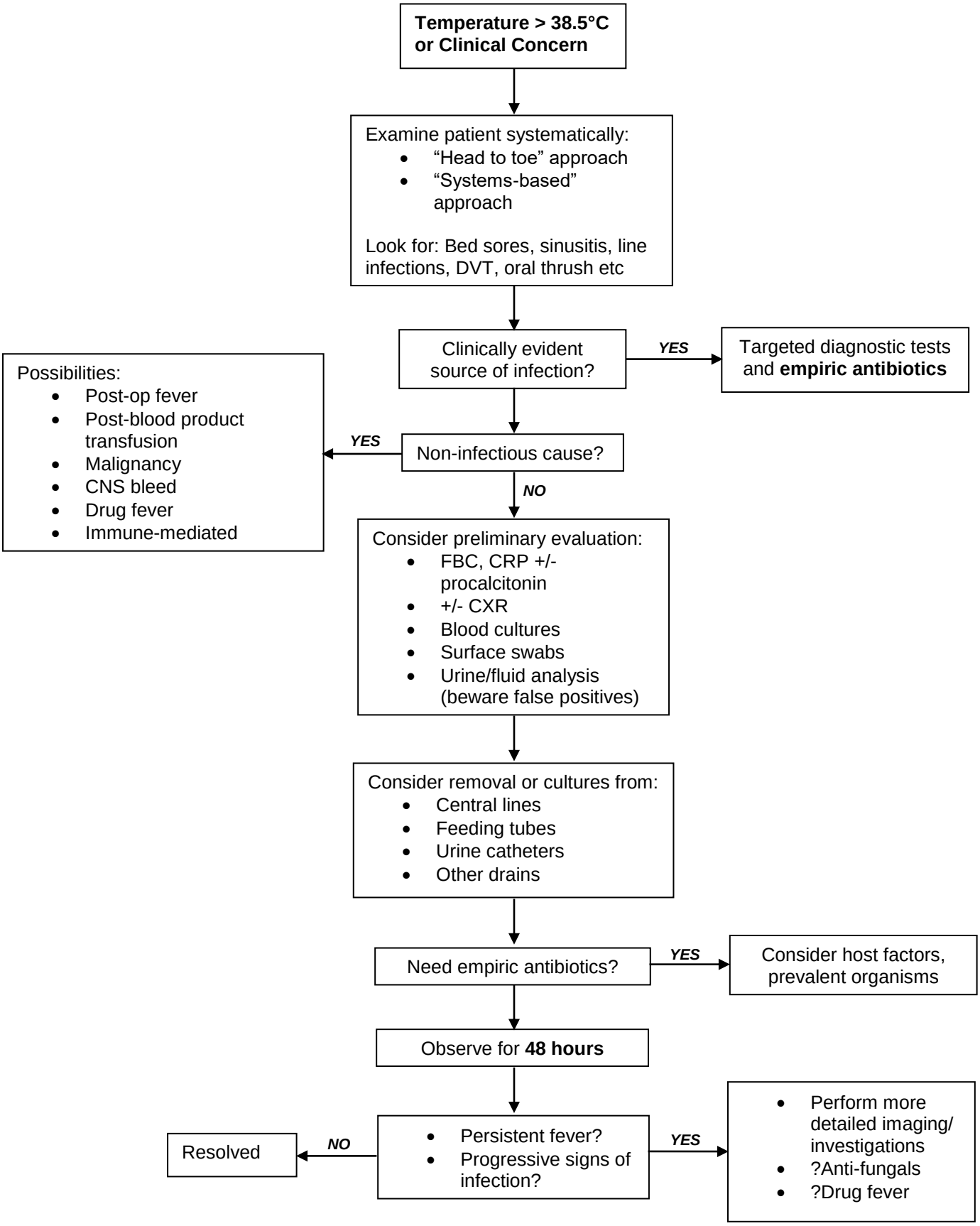
Fever is not uncommon in the paediatric ICU setting, and may or may not be as a result of an infection. Non-infectious causes of fever include inflammatory/ immune-mediated processes or post-operative fevers.

Post-operative patients may develop a fever (40-91% in some series); the majority of those that occur within 48 hours of surgery are non-infective in origin. The magnitude of the post-operative fever is not related to the risk of an infective process. A fever that occurs *after* 48 hours of surgery has a high risk of being related to an infection process.

GENERAL APPROACH

1. Primary prevention
2. Accurate and rapid diagnosis
3. Appropriate treatment
4. Secondary prevention




Temperature > 38.5°C or Clinical Concern
Examine patient systematically:
• "Head to toe" approach
• "Systems-based" approach
Look for: Bed sores, sinusitis, line infections, DVT, oral thrush etc
Clinically evident source of infection?
YES
Targeted diagnostic tests and empiric antibiotics
Possibilities:
• Post-op fever
• Post-blood product transfusion
• Malignancy
• CNS bleed
• Drug fever
• Immune-mediated
YES
Non-infectious cause?
NO
Consider preliminary evaluation:
• FBC, CRP +/- procalcitonin
• +/- CXR
• Blood cultures
• Surface swabs
• Urine/fluid analysis (beware false positives)
Consider removal or cultures from:
• Central lines
• Feeding tubes
• Urine catheters
• Other drains
Need empiric antibiotics?
YES
Consider host factors, prevalent organisms
Observe for 48 hours
Resolved
NO
• Persistent fever?
• Progressive signs of infection?
YES
• Perform more detailed imaging/ investigations
• ?Anti-fungals
• ?Drug fever

CHAPTER

Infections in the ICU

PAEDIATRIC SEPSIS

INTRODUCTION AND PATHOPHYSIOLOGY

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection, and remains a condition associated with significant morbidity and mortality in children.

The understanding of the pathophysiology of sepsis has been enhanced by the discovery of how the host innate immune system distinguishes self and non-self, by recognition of various microbial patterns and cellular products of microbial invasion or tissue injury. The recognition of these patterns (damage-associated molecular patterns [DAMPs] and pathogen-associated molecular patterns [PAMPs]) triggers a proinflammatory cascade, including the release of proinflammatory cytokines such as TNFα, IL-1 and IL-6 among others. This in turn causes propagation of the proinflammatory response, which is particularly exaggerated in sepsis.

An important consequence of the proinflammatory response is the activation of the coagulation cascade, resulting in a hypercoagulable state and formation of microthrombi. This can cause local perfusion defects, resulting in tissue hypoxia and organ dysfunction. Conversely, consumption of platelets and coagulation factors predisposes to bleeding risk. This phenomenon is referred to as disseminated intravascular coagulation. Cytokines may also cause depression of cardiac myocytes, further exacerbating tissue hypoperfusion and organ dysfunction.

Damage to the endothelial barrier, including the glycocalyx, results in leakage of vascular fluid, leucocyte migration, vasodilation, and the development of a procoagulant state. The widespread presence of the glycocalyx in organ microvasculature accounts for the disparate range of organs that may be affected. Indeed, sepsis can affect any organ in the body, with neurological (altered mental state), pulmonary (hypoxaemia), cardiovascular (shock), renal (oliguria and/or increased creatinine concentration), haematological (thrombocytopenia) and hepatic (hyperbilirubinaemia) dysfunction predominating.

It has also been increasingly recognised that a prolonged state of immunosuppression follows the initial proinflammatory condition, which may result in a less efficacious immune response to secondary bacterial, viral and fungal infections.

DEFINITIONS:

The current categories for stratifying a patient with sepsis are as follows:

Sepsis: Systemic inflammatory response syndrome (SIRS) (See age-specific vital sign and laboratory criteria in **Annex A**) in the presence of an infection.

Severe sepsis: Sepsis plus one of the following: (1) cardiovascular dysfunction; (2) acute respiratory distress syndrome (ARDS); (3) two or more organ dysfunctions (See criteria for organ dysfunction in **Annex B**).

Septic shock: Sepsis and cardiovascular organ dysfunction.

An infection includes any suspected or proven infection, including infections caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of

infection includes positive findings on clinical examination, imaging or laboratory investigations (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans).

APPROACH TO SEPSIS IN CHILDREN

Early recognition and appropriate management of sepsis are crucial in improving clinical outcome. An important consideration is that a significant proportion of children who develop sepsis have a pre-existing co-morbidity, and management should be tailored accordingly.

RECOGNITION:

Severe sepsis or septic shock should be considered in a patient with a suspected or proven infection and any of the following:

Altered mental status: This may include sleepiness, irritability, floppiness or lethargy.

Signs of cardiovascular dysfunction: Reduced peripheral perfusion, pale, cool or mottled skin, prolonged capillary refill time (CRT > 2sec), decreased urine output (<1 mL/kg/hr) or narrow pulse pressure

Respiratory distress: Tachypnoea, hypoxia, increased work of breathing out of proportion to a primary respiratory illness if present

Specific clinical and laboratory criteria for inclusion into the various sepsis categories are appended below for reference.

Two clinical phenotypes of shock have been described, namely cold and warm shock, although the ability to distinguish them using bedside observations alone has been poor. The identification of these phenotypes may influence subsequent management, e.g. inotrope choice.

Cold shock (characterized by low cardiac output and elevated systemic vascular resistance)**:** manifests as narrow pulse pressure, cool peripheries, prolonged capillary refill (more common in neonates and infants)

Warm shock (characterized by normal cardiac output and low systemic vascular resistance)**:** manifests as wide pulse pressure, bounding pulses, warm, flushed skin with rapid capillary refill (more common in older children and adolescents)

However, patients may evolve from one phenotype to another as illness progresses and some patients may have a mixture of features from both phenotypes.

PRINCIPLES OF MANAGEMENT:

Please use the flow chart (Annex C) below to guide stepwise-management of a child with severe sepsis.

Constant re-evaluation for deterioration, as well as for response to interventions, is crucial.

Laboratory investigations to consider:

Blood gas and lactate (serial measurement is more effective than a single reading), FBC, urea, electrolytes, creatinine, CRP, procalcitonin, PT/PTT
Blood glucose – treat hypoglycaemia if present
Blood cultures – aim to obtain blood cultures (aerobic x 1 routinely, PLUS anaerobic x 1 if intra-abdominal sepsis or other anaerobic infections suspected, or immunocompromised. For oncology patients or patients with central lines, to also perform aerobic and anaerobic central line cultures) before initiating antimicrobial therapy if it does not significantly delay commencement of antimicrobial administration.
Consider obtaining cultures form other sites, e.g., urine, CSF, wounds, if time allows and patient is stable.

Airway and breathing:

Give high flow oxygen in septic shock e.g. via non-rebreather mask, regardless of oxygen saturations in order to maximise oxygen delivery.

Consider early intubation and mechanical ventilation in children with excessive metabolic demands or fluid-refractory, catecholamine-resistant septic shock. Avoid etomidate as an induction agent (in view of risk of adrenal suppression).

Cardiovascular:

Up to 40-60 mL/kg in bolus fluid (10-20 mL/kg per bolus) can be given over the first hour. Fluid boluses should be dosed according to ideal body weight, and crystalloids should be used for initial resuscitation. Fluid resuscitation should be titrated to clinical markers of cardiac output, and discontinued if signs of fluid overload develop. Clinical markers of cardiac output include the following: heart rate, blood pressure, capillary refill time, level of consciousness and urine output. (Note: a satisfactory blood pressure in isolation is not an adequate endpoint for resuscitation)

Serial lactate measurement has been shown to be a useful adjunct to clinical assessment in assessing adequacy of resuscitation – persistently raised lactate may indicate incomplete haemodynamic resuscitation.

Consider insertion of an arterial line for monitoring of invasive blood pressure.

Fluid refractory shock (evidence of abnormal perfusion after 40-60ml/kg of fluid): Consider starting a peripheral inotrope early (see **Annex D** for guidance on dilution for peripheral administration) while awaiting central venous access – **please note that peripheral inotropes are only a short-term measure, and should be converted to central administration as soon as a central venous line is placed.** Consider adrenaline and noradrenaline as first-line agents in children with septic shock (see **Annex C**).

Catecholamine resistant shock: Consider hydrocortisone replacement. Dosing is as follows:

1) Parenteral hydrocortisone 100 mg/m^2 body surface area immediately, given IM or IV
2) Subsequent parenteral hydrocortisone to be given every 6 hours, at the following doses:
    a. 25mg/m^2 body surface area OR

b. If under 5 years: 1mg/kg body weight
c. If over 5 years: 0.5 mg/kg body weight

If adrenal insufficiency is suspected, hydrocortisone should be started as soon as possible. A synacthen test takes 1 hour to complete and should only be undertaken prior to giving the first dose of hydrocortisone if the ICU clinician considers it acceptable that the hydrocortisone can be started after completion of the test. Otherwise, a random serum cortisol level can be sent prior to starting hydrocortisone. Until more definitive endocrine testing is performed at a later time, the patient is deemed to have adrenal insufficiency if the random serum cortisol is <500 nmol/L, and hydrocortisone should be continued. Even if the random serum cortisol is >500 nmol/L, hydrocortisone can be continued if the clinical suspicion of adrenal insufficiency is high.

Antibiotics (see Empiric Antibiotic Choice in Annex E):

Aim to commence appropriate antimicrobial therapy as soon as possible, within 1 hour of recognition of septic shock, and within 3 hours of sepsis-associated organ dysfunction but without shock. Begin with empiric broad-spectrum therapy to cover all likely pathogens. Aim to narrow antimicrobial therapy coverage once pathogen(s) and sensitivities are available.

Antimicrobial choice should take into consideration the current KKH paediatric antimicrobial and nosocomial infection guidelines.

Source Control:
Early and aggressive source control should be a top priority in the management of the septic patient. This includes timely, appropriate evaluation, followed by drainage, debridement or other surgical interventions.

Nutrition:

Enteral nutrition is the preferred method of feeding. In a child with septic shock who has received adequate haemodynamic resuscitation and who no longer requires escalating doses of vasoactive agents, enteral feeding should not be withheld solely on the basis of vasoactive-inotropic medication administration. Parenteral nutrition may be withheld in the first 7 days of PICU admission in children with septic shock or other sepsis-associated organ dysfunction.

Adjunct therapies:

There is currently no evidence for routine empiric use of levothyroxine in children with septic shock and other sepsis-associated organ dysfunction in a sick euthyroid state. There is also no evidence for routine plasma exchange or intravenous immunoglobulin (IVIG). Use of these can be considered at the discretion of consultants in CICU or the relevant subspecialties.

Severe sepsis may progress to two pathological states that may require extra-corporeal membrane oxygenation (ECMO) support, these are acute respiratory distress syndrome (ARDS) and septic shock. ECMO may be considered for refractory shock despite adequate fluid resuscitation and inotropic support. It must be emphasized that ECMO is a supportive therapy that can provide macro-circulatory support, maintain oxygenation and carbon dioxide clearance, but it does not directly treat sepsis or its sequelae.

Our unit recommends early consideration of ECMO support if end-organ perfusion remains compromised despite high doses of multiple vaso-active drugs (e.g. adrenaline or noradrenaline infusions of 0.2 – 0.3 mcg/kg/min or vasopressin 0.04 – 0.06 u/kg/hr). When ECMO is employed in septic shock, central cannulation should be considered and higher ECMO flows (>150ml/kg/min for children <10kg or >2.4 L/min/m^2 for children > 10 kg) should be targeted.

Septic patients who progress to cardiac arrest or who develop significant bleeding from coagulopathy are poor candidates for extra-corporeal cardiopulmonary resuscitation or ECMO support.

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Annex A - Age-specific vital signs and laboratory variables for the diagnosis of SIRS

	Pediatric SIRS criteria (≥1 of the criteria from column 1 and column 2)							
	Column 1 (≥1 of the below criteria)				Column 2 (≥1 of the below criteria)			Cardiovascular dysfunction
	Core temperature (°C)		Leukocyte count (leukocytes × 10^3/mm^3)		Heart rate (beats/min)[a]		Respiratory rate[b]	
Age group	Hypothermia	Hyperthermia	Leukopenia	Leukocytosis	Bradycardia	Tachycardia	(breaths/min)	SBP (mmHg)
0 days to 1 week	<36	>38.5	NA	>34	<100	>180	>50	<65
1 week to 1 month	<36	>38.5	<6	>19.5	<100	>180	>40	<75
1 month to 1 year	<36	>38.5	<6	>17.5	<90	>180	>34	<100
2–5 years	<36	>38.5	<6	>15.5	NA	>140	>22	<94
6–12 years	<36	>38.5	<4.5	>13.5	NA	>130	>18	<104
13 to <18 years	<36	>38.5	<4.5	>11	NA	>110	>14	<117

depression over a 0.5 hr time period.

[b]Mean respiratory rate 2SD above normal for age or mechanical ventilation for acute process not related to underlying neuromuscular disease or the receipt of general anaesthesia.
Leucocyte count elevated or depressed for age (not secondary to chemotherapy-induced leucopenia) or 10% immature neutrophils.

Mathias B and Mira J. *Curr Opin Pediatr* 2016;28:380-387

Annex B – Criteria for Organ dysfunction

Cardiovascular dysfunction

Despite administration of isotonic intravenous fluid bolus ≥40 mL/kg in 1 hr

- Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 SD below normal for age[a]

OR

- Need for vasoactive drug to maintain BP in normal range (dopamine >5 μg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)

OR

- Two of the following
  Unexplained metabolic acidosis: base deficit >5.0 mEq/L
  Increased arterial lactate >2 times upper limit of normal
  Oliguria: urine output <0.5 mL/kg/hr
  Prolonged capillary refill: >5 secs
  Core to peripheral temperature gap >3°C

Respiratory[b]

- Pao_2/Fio_2 <300 in absence of cyanotic heart disease or preexisting lung disease

OR

- $Paco_2$ >65 torr or 20 mm Hg over baseline $Paco_2$

OR

- Proven need[c] or >50% Fio_2 to maintain saturation ≥92%

OR

- Need for nonelective invasive or noninvasive mechanical ventilation[d]

Neurologic

- Glasgow Coma Score ≤11 (57)

OR

- Acute change in mental status with a decrease in Glasgow Coma Score ≥3 points from abnormal baseline

Hematologic

- Platelet count <80,000/mm^3 or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)

OR

- International normalized ratio >2

Renal

- Serum creatinine ≥2 times upper limit of normal for age or 2-fold increase in baseline creatinine

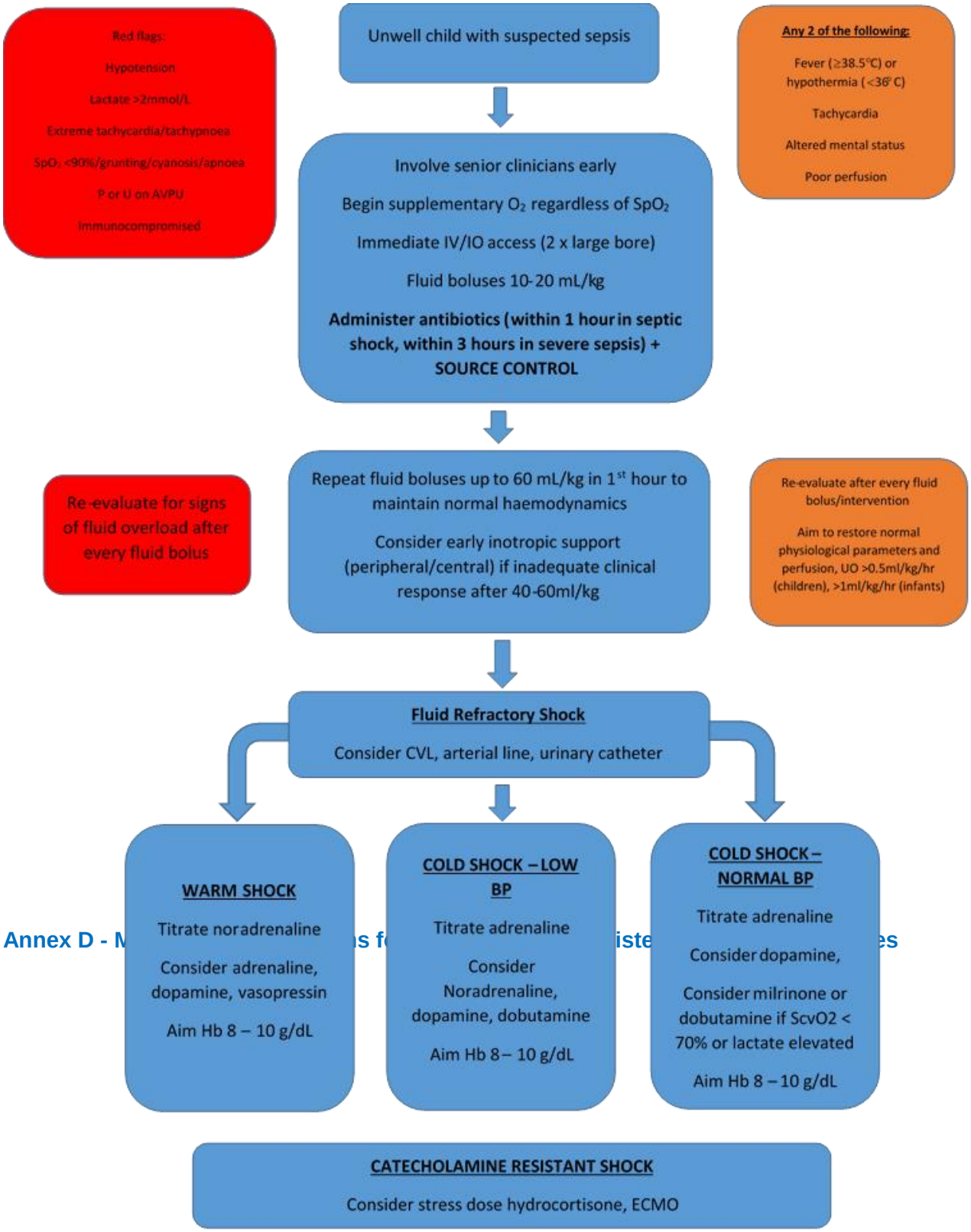
Hepatic

- Total bilirubin ≥4 mg/dL (not applicable for newborn)

OR

- ALT 2 times upper limit of normal for age

Annex C – Algorithm for Management of a Child with Severe Sepsis



Annex D - M ns f iste es

Drug Name	Maximum Peripheral Line Concentration	
Adrenaline	30	mcg/mL
Aminophylline	2.5	mg/mL
Alprostadil	5	mcg/mL
Amiodarone	2000	mcg/mL
Atracurium	500	mcg/mL
DOBUTamine (For weight exceeding 8 kg)	5000	mcg/mL
DOPamine (For weight exceeding 5 kg)	3200	mcg/mL
Dexmedetomidine	4	mcg/mL
Fentanyl (For weight exceeding 25 kg)	50	mcg/mL
Glyceryl Trinitrate	400	mcg/mL
Heparin	100	units/mL
Hydralazine	1000	mcg/mL
Insulin	1	unit/mL
Ketamine	1000	mcg/mL
Labetalol	1	mg/mL
Lignocaine	1000	mcg/mL
Magnesium Sulphate (Status Asthmaticus + Status Epilepticus)	200	mg/mL
Midazolam (For weight exceeding 16 kg)	1000	mcg/mL
Milrinone	200	mcg/mL
Morphine (For weight exceeding 50 kg)	1000	mcg/mL
Nitroprusside	200	mcg/mL
Noradrenaline	30	mcg/mL
Rocuronium (For weight exceeding 10 kg)	5	mg/mL
Salbutamol	200	mcg/mL
Thiopental	4	mg/mL
Vasopressin (DI)	20	mU/mL

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Annex E – Empiric Antibiotic Choice

(Please use in conjunction with KKH Paediatric Antimicrobial Guidelines)

Factors affecting the choice of initial empirical antibiotics include the following:

Host Factors:

- Immunocompromised: need to consider broad spectrum bacterial, fungal +/- viral coverage
- Severely ill: need broad spectrum empiric coverage as the window of opportunity is small, also need to consider renal/ hepatic dysfunction

Environmental Factors:

- Prevalent organisms: utility of antibiograms

Drug Factors:

- Toxicity, side effects, drug-drug interactions

Possible initial regimes in severe nosocomial infections

Blood stream Infection (especially if central venous catheter in-situ):

- (3rd or 4th generation cephalosporin or beta-lactam/ beta-lactamase inhibitor or carbapenem) +/- aminoglycoside +/- vancomycin (or linezolid) +/- amphotericin

Hospital acquired pneumonia/ ventilator associated pneumonia (late onset):

- (Anti-pseudomonal cephalosporin or beta-lactam/beta-lactamase inhibitor or carbapenem) +/- aminoglycoside (or fluoroquinolone) +/- vancomycin (or linezolid).
- Consider anti-fungals

Urinary tract infection (especially in those with indwelling catheters):

- (3rd or 4th generation cephalosporin or beta-lactam/beta-lactamase inhibitor or carbapenem) + aminoglycoside (+/- anti-fungals)

Surgical site infection:

- (Anti-pseudomonal beta-lactam/beta-lactam inhibitor or carbapenem)+/- vancomycin (+ metronidazole for intra-abdominal infection)

CNS device infection:

- Vancomycin + (anti-pseudomonal cephalosporin or beta-lactam/beta lactamase inhibitor)

Note: As part of the MOH/KKH Antibiotic Stewardship Programme (ASP), audits are carried out on the use of beta-lactam/beta-lactamase inhibitors, carbopenems, 4th generation cephalosporins and vancomycin; please refer to the relevant guidance when prescribing these antimicrobials.