CG009 Severe Sepsis (Adults and Children)

<table>
<tr><th colspan="4">1. Key Recommendations for operational use</th></tr>
<tr><td colspan="4">For use by: ScotSTAR Adult and Paediatric, Referring centres. Internet: Yes</td></tr>
<tr><td rowspan="3">1</td><td rowspan="3">Diagnosis</td><td colspan="2">• SIRS, NEWS, MEWS or age appropriate PEWS can be helpful as a screening tool for sepsis but be aware of their limitations.
• Consider treating as sepsis if patient has suspected infection with at least 2 of the following:</td></tr>
<tr><td>Adults</td><td>Children</td></tr>
<tr><td>- Temperature > 38˚C or < 36˚C.
- Heart rate > 90/min.
- Respiratory rate > 20/min.
- WBC > 12 x 10^9/L.</td><td>- Temperature > 38˚C or < 36˚C.
- Inappropriate tachycardia (use PEWS chart for age specific ranges).
- Altered mental state.
- Capillary refill >2s.</td></tr>
<tr><td colspan="3">• Reduce threshold for treatment in high risk groups (eg immunocompromise).
• Look for organ dysfunction and hypotension to guide further management.</td></tr>
<tr><td>2</td><td>Oxygen</td><td colspan="2">• Give oxygen then titrate down to SpO_2 94-98%.</td></tr>
<tr><td>3</td><td>IV access</td><td colspan="2">• Insert the widest bore cannula feasible.
• Take blood cultures.
• Measure blood lactate if available.
• Use intraosseous access if attempts at IV cannulation are unsuccessful.</td></tr>
<tr><td>4</td><td>Microbiological sampling</td><td colspan="2">• In addition to blood cultures, take any other samples as feasible, e.g. respiratory secretions, urine, wound swabs.</td></tr>
<tr><td>5</td><td>Antimicrobial therapy</td><td colspan="2">• Give antibiotics as soon as possible after recognition of sepsis:
- within one hour if high likelihood of septic shock.
• Give empiric broad spectrum with one or more antimicrobials to cover all likely pathogens:
- including bacterial and potentially fungal and viral coverage.
- consider need for empirical MRSA / multi-drug resistant pathogens / antifungals.
• Consider antibiotic allergy in particular to penicillins and cephalosporins.
- previous rash without anaphylaxis is not a contraindication to administration.
• Use local guidelines for empiric antibiotic administration.
• If in doubt give:
- Neonate <72hrs: IV Benzylpenicillin 25mg/kg + IV Gentamicin 5mg/kg.
- Neonate >72hrs: IV Cefotaxime 50mg/kg + IV Gentamicin 5mg/kg + IV Amoxicillin 50-100mg/kg (up to 1g).
- Child (>1 month): IV Cefotaxime 50mg/kg + IV Gentamicin 7mg/kg if severe.
- Adults 2g IV Ceftriaxone.
• Avoid ceftriaxone in neonates.</td></tr>
</table>

6	Initial Fluids	• For patients with sepsis induced hypoperfusion or septic shock: - Adults: consider at least 30 ml/kg within the first 3 hours. - Children: 10ml/kg aliquots to a total of 40-60ml/kg over the first hour. • Use crystalloid, either balanced (eg Hartmann's, Plasma-lyte148) or 0.9% saline. - do not give colloids or starches. • Assess for signs of fluid overload.
7	Monitoring	• Insert urinary catheter and monitor urine output hourly. • Consider inserting arterial line if hypotensive at any point. • Do not insert central line specifically to measure central venous pressure.
8	Vasoactive medication	• Consider vasoactive drugs if resistant to initial fluid resuscitation: - if patient continues to have evidence of abnormal perfusion after fluid or there are signs of fluid overload without signs of improved perfusion. • Do not delay vasoactive drugs awaiting central access - start peripherally. • If infusing vasoactive medications through a peripheral vein: - use only for a short period of time and into a vein proximal to the wrist. - monitor the site carefully for signs of extravasation. • Consider inserting a central venous line balanced against: - time required, asepsis, coagulopathy, thrombocytopenia, X-ray availability. - central access in children can be challenging and age/size specific lines are needed. • In adults, start a noradrenaline infusion. - through a central line, use 4mg/**50**ml dilution (80 microgrammes/ml) in 5% glucose. - through a peripheral line, use 4mg/**250ml** dilution (16 microgrammes/ml). • Consider using adrenaline (or noradrenaline plus dobutamine) with demonstrable or suspected left ventricular systolic dysfunction. - use 4mg/50ml dilution (80 microgrammes/ml) in 5% glucose centrally or peripherally. • In children, start an adrenaline infusion: - add 0.3mg/kg adrenaline to 50mls 5% glucose. - start at 1ml/hr which is 0.1 microgram/kg/min. - if using peripherally, use this formula to a maximum concentration of 4mg/50ml (80 microgrammes/ml), approximately a 13kg child. • Target mean arterial pressure (MAP) of 65mmHg or age appropriate MAP in children. • See **CG011 Drug Infusions** for stronger concentrations of adrenaline or noradrenaline to be given centrally only and for information on dobutamine.

9	Ongoing fluid therapy	• Use crystalloids for subsequent intravascular volume replacement. • To guide ongoing intravenous fluid administration: - do not use heart rate, systolic blood pressure or central venous pressure alone. - assess organ perfusion, eg level of consciousness and urine output. - assess tissue perfusion with capillary refill time, including demarcation (cold) line. • Use dynamic parameters as feasible, eg response to passive leg raise in adults or older children. - static leg raises are ineffective in smaller children. • Repeat serum lactate to guide effectiveness of fluid resuscitation. • Hepatomegaly may indicate fluid overload in children, but has many other causes.
10	Glucose	• Avoid hypoglycaemia - children at higher risk. - aggressively treat blood glucose levels <4mmol/L with bolus of 2ml/kg 10% Glucose. • In children, use caution in treating hyperglycaemia with an insulin infusion: - it is usually not required. - consider taking expert advice. • In adults, consider treating persistent hyperglycaemia with an insulin infusion provided the infusion can be reliably managed to avoid hypoglycaemia.
11	Steroids	• Consider IV Hydrocortisone 50mg in adults or 1mg/kg in children if shock is refractory to fluids and vasoactive medication. • Give IV Hydrocortisone to patients who have had any recent systemic steroid therapy: - 100mg in adults or 1mg/kg in children.

2. Document History			
Reference Number	CG009		
Version	2		
Writing group (Lead author in bold)	**Kathryn Bennett**	Intensivist	EMRS West
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Distribution	BASICS Scotland		✓
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	SAS	Air Ambulance	✓
		Specialist Services Desk	X
	ScotSTAR	EMRS West	✓
		EMRS North	✓
		Paediatric	✓
		Neonatal	X
	Tayside Trauma Team		X

3. Scope and purpose

- Overall objectives:

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection which is associated with an in-hospital mortality greater than 10%. Septic shock is a subset of sepsis with circulatory and cellular / metabolic dysfunction associated with a greater risk of mortality than with sepsis alone. Sepsis and septic shock are medical emergencies and treatment and resuscitation should begin immediately. The aim of this guideline is to summarise the early management and resuscitation of adults and children with sepsis or septic shock that can be applied to a remote and rural healthcare setting, mindful of variable resources between these facilities.

- Statement of intent:

This guideline is not intended to be construed or to serve as a standard of care. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. Clinicians using this guideline should work within their skill sets and usual scope of practice.

- Feedback:

Comments on this guideline can be sent to: sas.cpg@nhs.scot

- Equality Impact Assessment:

Applied to the ScotSTAR Clinical Standards group processes.

- Guideline process endorsed by the Scottish Trauma Network Prehospital, Transfer and Retrieval group.

SCOTTISH TRAUMA NETWORK

4. Explanatory Statements

<table>
<tr><th colspan="2">4.1 Diagnosis</th><th>Authors' recommendation</th><th>Level [Reference]</th></tr>
<tr><td colspan="2">• SIRS, NEWS, MEWS or age appropriate PEWS can be helpful as a screening tool for sepsis but be aware of their limitations for the early identification of infection induced organ dysfunction.
• Consider treating as sepsis if patient has suspected infection with at least 2 of the following:</td><td></td><td rowspan="6">Guideline [1,6,13]</td></tr>
<tr><td>Adults</td><td>Children</td><td></td></tr>
<tr><td>- Temperature > 38˚C or < 36˚C.
- Heart rate > 90/min.
- Respiratory rate > 20/min.
- WBC > 12 x 10⁹/L.</td><td>- Temperature > 38˚C or < 36˚C.
- Inappropriate tachycardia (use PEWS chart for age specific ranges).
- Altered mental state.
- Capillary refill >2s.</td><td></td></tr>
<tr><td colspan="2">• Reduce threshold for treatment in high risk groups (eg immunocompromise).
- <3 months old.
- Immunocompromised.
- Indwelling lines.
- Recent surgery.
- Complex neurodisability.
- Significant parental concern.</td><td></td></tr>
<tr><td colspan="2">• Look for organ dysfunction and hypotension to guide further management.
• Severe sepsis criteria (SIRS plus organ dysfunction, hypotension or hypoperfusion):
- lactic acidosis.
- systolic BP < 90mmHg or Systolic BP drop ≥ 40mmHg of normal.
• Septic shock criteria (severe sepsis with hypotension despite adequate volume resuscitation).
• Multiple organ dysfunction syndrome criteria:
- evidence of ≥ 2 organs failing.</td><td></td></tr>
<tr><td colspan="2">Sepsis is life-threatening organ dysfunction due to a dysregulated host response to infection. This is a medical emergency requiring immediate treatment and resuscitation. The importance of regular assessment of response to treatment cannot be over-emphasised.</td><td></td></tr>
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4.2 Oxygen	**Authors' recommendation**	**Level [Reference]**
• *Give oxygen then titrate down to SpO_2 94-98%.* Deliver supplemental oxygen and monitor oxygenation continuously with pulse oximetry. Intubation and mechanical ventilation may be required to support the increased work of breathing or to manage the altered mental status that typically accompanies sepsis. The role of conservative vs liberal oxygen targets in ventilated patients is unresolved [1].	Strong	Guideline [2]
4.3 IV Access		
• *Insert the widest bore cannula feasible.*	GPP	
• *Take blood cultures.*	Strong	Guidelines [1,7]
• *Measure blood lactate if available.* Serum lactate is useful to guide resuscitation but is diagnostically is insufficient to rule in or rule out sepsis.	Conditional	Guidelines [1,7]
• *Use intraosseous access if attempts at IV cannulation are unsuccessful.* Peripheral IV access is often challenging in children with sepsis. Intraosseous access is a rapid and effective means of initialising treatment. The preferred site of insertion in children is the medial aspect of the proximal tibia 1cm below the tibial tuberosity.	Conditional	Guideline [7]
4.4 Microbiological sampling		
• *In addition to blood cultures, take any other feasible samples, e.g. respiratory secretions, urine, wound swabs.* Obtain appropriate microbiologic cultures (including blood) before starting antimicrobial therapy in patients with suspected sepsis or septic shock. Do not delay administration of antimicrobials. Taking all appropriate microbiology samples may not be practical prior to transfer.	Strong	Guidelines [1,7]

4.5 Antimicrobial therapy	Authors' recommendation	Level [Reference]
• *Give antibiotics as soon as possible after recognition of sepsis:* - *within one hour if high likelihood of septic shock.* • *Give empiric broad spectrum with one or more antimicrobials to cover all likely pathogens:* - *including bacterial and potentially fungal and viral coverage.* - *consider need for empirical MRSA / multidrug resistant pathogens / antifungals.* • *Use local guidelines for empiric antibiotic administration.* The rapidity of administration is central to the beneficial effect of appropriate antimicrobials. Risk-benefit ratio favours the rapid administration of antimicrobials even if it is not possible to obtain cultures promptly. The initial selection of antimicrobial therapy should be broad enough to cover all likely pathogens and choice depends on complex issues related to the patient's medical history and local epidemiological factors. Consider potential drug intolerances and toxicities.	Strong	Guideline [1,7]
• *Consider antibiotic allergy in particular to penicillins and cephalosporins.* - *previous rash without anaphylaxis is not a contraindication to administration.*	GPP	
• *Use local guidelines for empiric antibiotic administration.*	Strong	Guideline [7]
• *If in doubt, and assuming no penicillin allergy, give:* - *Neonate <72hrs: IV Benzylpenicillin 25mg/kg + IV Gentamicin 5mg/kg.* - *Neonate >72hrs: IV Cefotaxime 50mg/kg + IV Gentamicin 5mg/kg + IV Amoxicillin 50-100mg/kg.* - *Child (>1 month): IV Cefotaxime 50mg/kg + IV Gentamicin 7mg/kg if severe.* Antibiotic selection for community acquired sepsis in paediatrics varies by age due to the differing prevalence of causative organisms. Infants <72 hours old are at increased risk of Streptococcal and E. coli infection and so treated with Benzylpenicillin and Gentamicin. Infants >72 hours old should receive IV Amoxicillin in addition to Cefotaxime & Gentamicin to cover for possible Listeria infection. Sepsis in children is mostly due to gram-negative or gram-positive bacteria which is covered by Cefotaxime. Gentamicin can be added if the child is critically ill to provide extended gram-negative cover.		Guideline [8]
- *Adults 2g IV Ceftriaxone.*	GPP	
• *Avoid ceftriaxone in neonates.* Avoid ceftriaxone in neonates as it displaces bilirubin from albumin and it interacts with calcium which precipitates, especially in small cannulae.	GPP	

4.6 Initial fluids	**Authors' recommendation**	**Level [Reference]**
• *For patients with sepsis induced hypoperfusion or septic shock:* - *Adults: consider at least 30 ml/kg within the first 3 hours.*	Conditional	Guideline [1]
- *Children: 10ml/kg aliquots to a total of 40-60ml/kg over the first hour.*		Guidelines [6,7,13]
Timely, effective fluid resuscitation is crucial for the stabilisation of sepsis-induced hypoperfusion in sepsis and septic shock. Whilst protocolised fluid resuscitation has not been shown to be of benefit, this volume of fluid enables initiation of resuscitation whilst obtaining more specific information more precise measurements of haemodynamic status.		
• *Use crystalloid, either balanced (eg Hartmann's, Plasma-lyte148) or 0.9% saline.* - *do not give colloids or starches.* There is no evidence of any clear benefit of colloids compared to crystalloid solutions in sepsis; there may be harm associated with the use of synthetic starches. Albumin (if available) is the colloid of choice if it is necessary for intravascular volume replacement as it has no association with harm in sepsis [1]. Recent trials in adults [10,11] have shown that balanced crystalloid solutions confer no benefit over 0.9% saline.	Strong	Guidelines [1,7] 1++ [10,11]
• *Assess for signs of fluid overload.* The volume can be reduced if there is concern regarding pulmonary oedema or cardiac failure. The response to all fluid resuscitation should be noted. Identifying fluid overload is especially difficult in children but signs include; worsening respiratory status, radiographic evidence of pulmonary oedema or new or expanding hepatomegaly.		Guideline [1,7]
4.7 Monitoring		
• *Insert urinary catheter and monitor urine output hourly.*	GPP	
• *Consider insertion of arterial line if hypotensive at any point.* In shock states, estimation of blood pressure using a cuff may be inaccurate. Use of an arterial cannula provides a more accurate and reproducible measurement of arterial pressure and also allows beat-to-beat analysis.	Conditional	Guideline [1]
• *Do not insert central line specifically to measure CVP.* The use of CVP alone to guide fluid resuscitation is no longer justified because the ability to predict a response to a fluid challenge when the CVP is with normal range is limited. Central line insertion should be reserved for difficult IV access or administration of vasoactive medications.	Conditional	Guideline [1] 1++ [3]

4.8 Vasoactive medication	Authors' recommendation	Level [Reference]
• *Consider vasoactive drugs if resistant to initial fluid resuscitation:* - *if patient continues to have evidence of abnormal perfusion after fluid or there are signs of fluid overload without signs of improved perfusion.*	Conditional	Guideline [7]
• *Do not delay vasoactive drugs awaiting central access - start peripherally.* • *If infusing vasoactive medications through a peripheral vein:* - *use only for a short period of time and into a vein proximal to the wrist.* - *monitor the site carefully for signs of extravasation* • *Consider inserting a central venous line balanced against:* - *time required, asepsis, coagulopathy, thrombocytopenia, X-ray availability.* - *central access in children can be challenging and age/size specific lines are required.* Vasoactive medications should normally be infused through a central line. In certain circumstances, it may be necessary to administer through a cannula in a large peripheral vein. These circumstances include the need for immediate resuscitation or time pressure to move the patient.	Conditional	Guidelines [1,7,12]
• *In adults, start a noradrenaline infusion.* - *through a central line, use 4mg/**50**ml dilution (80 microgrammes/ml) in 5% glucose.* - *through a peripheral line, use 4mg/**250ml** dilution (16 microgrammes/ml).* • *Consider using adrenaline (or noradrenaline plus dobutamine) with demonstrable or suspected left ventricular systolic dysfunction.* - *use 4mg/50ml dilution (80 microgrammes/ml) in 5% glucose centrally or peripherally.* Both agents are suggested although there is a relative absence of evidence that the addition of either to a noradrenaline infusion is beneficial.	Conditional	Guidelines [1,12]
• *In children, start an adrenaline infusion:* - *add 0.3mg/kg adrenaline to 50mls 5% glucose.* - *start at 1ml/hr which is 0.1 microgram/kg/min.* - *if using peripherally, use this formula to a maximum concentration of 4mg/50ml (80 microgrammes/ml), approximately a 13kg child.* Adrenaline and noradrenaline are both widely available and effective at treating fluid resistant hypotension in children. Adrenaline has been shown to be associated with a lower risk of mortality compared with Dopamine. Use of noradrenaline has not been studied in children with septic shock.	Conditional	Guidelines [6,7]

• *Target mean arterial pressure (MAP) of 65mmHg or age appropriate MAP in children.* MAP is a key determinant of mean systemic filling pressure which, in turn, is the main driver of venous return and cardiac output. Increasing MAP therefore usually results in increased tissue blood flow. A target MAP of 65-70 mmHg is suitable for most adult patients, however, a higher MAP can be considered in patients with pre-existing hypertension who may be dependent on a higher MAP for adequate end-organ perfusion. The paediatric SSC guideline [7] does not offer consensus on target MAP (by age appropriate mean percentile in children).	Strong	Guidelines [1,7]
• See **CG011 Drug Infusions** for stronger concentrations of adrenaline or noradrenaline to be given centrally only and for information on dobutamine.		

4.9 Ongoing fluid therapy	**Authors' recommendation**	**Level [Reference]**
• *Use crystalloids for subsequent intravascular volume replacement.* As with the initial resuscitation, there is an absence of any clear benefit of colloid or starch solutions compared to crystalloid solutions in sepsis.	Strong	Guideline [1]
• *To guide ongoing intravenous fluid administration:* - *do not use heart rate, systolic blood pressure or central venous pressure alone.* These static measures alone are poor indicators of fluid status and are no longer recommended; preference is for dynamic measures outlined below.	Strong	Guideline [1] 1++ [3]
- *assess organ perfusion, eg level of consciousness and urine output.*	Conditional	Guidelines [1,7]
- *assess tissue perfusion with capillary refill time, including demarcation (cold) line.* When advanced haemodynamic monitoring is not available, alternative measures of organ perfusion may be used to evaluate the effectiveness and safety of volume administration. Temperature of the extremities, skin mottling and capillary refill time have been validated and shown to be reproducible signs of tissue perfusion [5].	Conditional	Guidelines [1,7] 1++ [5]
• *Use dynamic parameters as feasible, eg response to passive leg raise in adults or older children.* - *static leg raises are ineffective in smaller children.* Following initial fluid resuscitation, additional fluids should be guided by frequent reassessment of dynamic measures which have demonstrated better diagnostic accuracy at predicting fluid responsiveness compared with static techniques. The evidence base for fluid responsiveness is difficult to implement in the remote / retrieval environment since it depends on directly measuring cardiac output. Easily applied dynamic measures include passive leg raising or fluid challenges against systolic pressure or pulse pressure.	Conditional	Guideline [1] 4 [4]

• *Repeat serum lactate to guide effectiveness of fluid resuscitation.* Serum lactate is an important biomarker of tissue hypoxia and dysfunction. However, consider other causes of an elevated lactate. Resuscitation should aim to decrease lactate but normal levels may not be achievable.	Conditional	Guidelines [1,7]
• *Hepatomegaly may indicate fluid overload in children, but has many other causes.*	Conditional	Guideline [7]

4.9 Glucose	**Authors' recommendation**	**Level [Reference]**

• *Avoid hypoglycaemia - children at higher risk.*
  - *aggressively treat blood glucose levels <4mmol/L with bolus of 2ml/kg 10% Glucose.*
• *In children, use caution in treating hyperglycaemia with an insulin infusion:*
  - *it is usually not required.*
  - *consider taking expert advice.*
Primary aim of treatment should be to prevent hypoglycaemia therefore treating hyperglycaemia with an insulin infusion should be undertaken with caution
Meta-analyses have shown no reduction in mortality associated with tight glycaemic control in children with sepsis but have demonstrated a substantially higher risk of insulin-induced hypoglycaemia. Hypoglycaemia in children with septic shock is associated with poorer long term developmental outcomes.
		Guideline [7]
		1^{++}
		[9]

• *In adults, consider treating persistent hyperglycaemia with an insulin infusion provided the infusion can be reliably managed to avoid hypoglycaemia.* Treatment of hyperglycaemia (two or more blood glucose measurements >10mmol/L) is a strong recommendation from the SSC [1]. However, this needs to be applied to the practicalities of managing an insulin infusion in transit and the relatively short time periods involved. Intensive insulin therapy is not associated with a mortality benefit in sepsis but is associated with a higher incidence of hypoglycaemia. Treatment should avoid hyperglycaemia, hypoglycaemia and wide swings in glucose levels. The continuation of insulin infusions, especially with the cessation of nutrition, has been identified as a risk factor for hypoglycaemia.	Conditional	Guideline [1]

4.11 Steroids	Authors' recommendation	Level [Reference]
• *Consider IV Hydrocortisone 50mg in adults or 1mg/kg in children if shock is refractory to fluids and vasoactive medication.* In context of the remote / retrieval environment, steroids are not required routinely for patients on vasopressors but can be considered in patients with escalating vasopressor requirements, particularly if there are delays to definitive care. Steroids may reduce the overall duration of vasopressor therapy but do not alter mortality. The SSC suggestion is to start when the dose of adrenaline or noradrenaline exceeds 0.25 microgram/kg/min. (This equates to 15ml/hr of 80microgrammes/ml dilution for an 80kg patient).	Conditional	Guideline [1]
There is currently no evidence to support or refute the benefits of adjunctive corticosteroids in paediatric sepsis.		Guideline [7]
• *Give IV Hydrocortisone to patients who have had any recent systemic steroid therapy:* - *100mg in adults or 1mg/kg in children.*	GPP	

5. References

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