Nepal Paediatric Society Clinical Guidance for Management of Sepsis and Septic Shock in the Paediatric Intensive Care Units in Nepal

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ABSTRACT

Justification: Sepsis is a major cause of morbidity and mortality in Nepal. There is a lack of standardisation in the management of severe sepsis and septic shock. Additionally, international guidelines may not be completely applicable to resource limited countries like Nepal.

Objective: Create a collaborative standardised protocol for management of severe sepsis and septic shock for Nepal based on evidence and local resources.

Process / **Methods:** Paediatricians representing various paediatric intensive care units all over Nepal gathered to discuss clinical practice and delivery of care of sepsis and septic shock under the aegis of Nepal Paediatric Society. After three meetings and several iterations a standardised protocol and algorithm was developed by modifying the existing Surviving Sepsis Guidelines to suit local experience and resources.

Recommendations: Paediatric sepsis and septic shock definitions and management in the early hours of presentation are outlined in text and flow diagram format to simplify and standardise delivery of care to children in the paediatric intensive care setting. These are guidelines and may need to be modified as necessary depending on the resources availability and lack thereof. It is recommended to analyse data moving forward and revise every few years in the advent of additional data.

INTRODUCTION

Paediatric critical care is a relatively new field in Nepal, with around 25 stand-alone paediatric intensive care units (PICU).¹ A report from 2016 stated that there are less than 100 PICU beds available for critically ill children in Nepal with over 60% concentrated in and around the capital city.² The report describes the lack of trained critical care manpower, including nurses and physicians; and insufficient equipment, laboratory, and radiology services. Ongoing training in paediatric critical care is also inadequate. Additionally, even within Nepal significant disparities exist: majority of the nation is rural with difficult terrain and transportation, and further lack of resources and income exist. Access to health care, let alone sophisticated monitoring and management, is not feasible.¹ Appropriate transport of the critically ill child is almost non-existent in regions outside a few major cities, and even in these cities it is not well established. There is increased variability in critical health care delivery, including sepsis management, which, in several instances is not based on evidence and standard of care.² This impacts the morbidity and mortality of critically ill children. Additionally, international sepsis protocols are geared toward high resource nations with differing epidemiology, skills, resources, and practices and may lack relevance to countries like Nepal.³

PURPOSE

The primary objective of this clinical guidance document is to put forth consensus definitions and create a standardised protocol for severe sepsis and septic shock that is ⁴:

1. Collaborative among paediatricians working in various PICUs in Nepal

2. Feasible in view of the monitoring and management resources available

3. Adapted from Surviving Sepsis Guidelines

This guidance is mainly for management in the PICU and high dependency unit (HDU). However, it is targeted towards all physicians and healthcare workers managing children in inpatient, emergency, urgent care settings all over Nepal. In facilities that lack PICUs or HDUs this document should guide early management of sepsis and septic shock prior to transport to a higher level of care.

METHODOLOGY

Supporting organisation, selection of panel members and procedure

This clinical guideline has been prepared under the aegis of Nepal Paediatric Society. Hospitals all over Nepal were screened to identify those with PICUs. At least one paediatrician from each of the PICUs were invited to attend seminars to discuss and prepare the document. International guidelines and recommendations were reviewed. After successive iterations, the final document was agreed upon by the panel.

References used for discussions

This clinical guideline for sepsis and septic shock for Nepal was prepared by reviewing and adapting from standardised guidelines, viz., American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Paediatric and Neonatal Septic Shock 2017⁵ and Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children 2020.⁴ Other documents that were referenced were World Health Organisations publications on sepsis.^{6,7} Additionally, since several recommendations in these international guidelines may not be feasible in the context of locally available resources, experience of paediatricians working in PICUs across Nepal was taken into consideration, and existing 'septic shock management protocols' of different hospitals were also reviewed.

CLINICAL GUIDELINE (APPENDIX 1)

Definitions

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defined sepsis in adults as life-threatening organ dysfunction caused by dysregulated host response to infection; and septic shock as a subset of sepsis with profound circulatory, cellular and metabolic abnormalities associated with a greater risk of mortality.⁸ However, this definition lacks practicality in identifying and managing children with sepsis at the bedside in resource limited regions, including Nepal.⁹

For the purposes of this document and ease of identifying septic shock in children the panel came to a consensus to define septic shock as: suspected or confirmed infection with "Triad of fever or hypothermia, tachycardia, and signs of decreased tissue perfusion. The latter is defined as cold extremities, weak pulse volume, and prolonged capillary refill⁷ plus change in mental status [irritability, inappropriate crying, drowsiness, confusion, poor interaction with parents, lethargy, or becoming unarousable] and decrease in urine output, with or without low blood pressure" (Table 1).

Early Recognition

The panel recommends all facilities including PICU, HDU, inpatient wards, emergency rooms, and urgent care facilities to establish tools for early recognition of septic shock and deterioration in patient status. Such tools can be an objective evaluation of patient to assess for severity of illness and deterioration in status. Nursing staff can be taught to use such tools at dedicated intervals and alert physicians if a certain score is used. The Monaghan Paediatric Early Warning Signs (PEWS)^{10,11} is a widely used and validated tool which may have high feasibility in resource limited regions since this tool is based entirely on physiologic parameters, including behaviour, cardiologic status, and respiratory status, and has no requirement for laboratory data.

Abnormal vital signs according to age

Table 2 demonstrates age specific upper and / or lower limits of heart rate to define tachycardia and bradycardia, respiratory rate to define tachypnea, normal systolic BP and mean arterial pressure [MAP], and systolic BP to define hypotension (absolute indication for fluid bolus in septic shock).

Table 1. The clinical diagnosis of septic shock

	The clinical diagnosis of septic shock					
1	Suspected infection manifested by hypothermia (< 96.8 F) or hyperthermia (>100.4 F)					
AND						
2	Hypotension which is characterized as					
	a. Low systolic BP					
	OR					
	b. Clinical signs of inadequate tissue perfusion including <u>all</u> of the following ⁷ :					
	i. Prolonged capillary refill greater than 3 seconds					
	ii. Mottled, cool extremities					
	iii. Weak fast pulse					
3	Decreased urine output less than 0.5 mL/kg/hour for over 6 - 8 hours. AND / OR Decreased or altered mental status					

Age group	HR (bpm): Mean (range)	RR tachypnea: (breaths / min)	Systolic BP, mmHg: Normal 5th percentile	Systolic BP, mmHg: Hypotension ^{4,7} Indication for fluid bolus in septic shock	MAP, mmHg Hypotension ¹²
Up to 1 months	140 [100 – 190]	> 60	60	< 50	< 1.5 x age in years + 40
> 1 month to 1 year	130 [80 - 180]	> 50	70	< 50	< 1.5 x age in years + 40
1-5 years	80 [60 - 140]	> 40	70 + (age x 2): up to 10 years	< 60	< 1.5 x age in years + 40
> 5 years	80 [60 - 130]	> 30	90: > 10 years	< 70	< 1.5 x age in years + 40

Table 2. Age specific vital signs

Goals of management

- 1. Maintain or restore airway, oxygenation, and ventilation.
- Maintain or restore circulation: normal perfusion, blood pressure, urine output > 1 ml/ kg/hour
- 3. Maintain or restore threshold heart rate
- 4. Avoid fluid overload
- 5. Control source of infection
- 6. Stabilisation and maintenance

Laboratory Tests

Daily assessments of complete blood count (CBC), metabolic screen [sodium (Na), Potassium (K), calcium (ionised if possible, iCa)], dextrose stix (RBS), serum albumin, blood urea (BUN), creatinine (Cr), liver function test (LFT), blood gas (if available), coagulation profile (if abnormal).

Microbiology: Blood culture (C/S), urine routine (RME) and C/S, disease specific serology.

Inflammatory marker: C-reactive protein (CRP)

Intravenous Access

As soon as the patient arrives to the facility, intravenous (IV) access needs to be attempted. At least two large bore catheters are required. If three attempts are unsuccessful, intraosseus (IO) catheter may be placed and used with the decision to retry to place IV at a subsequent time.

Monitoring

Monitoring and reassessment are key in avoiding deterioration and complications of therapy, and evaluation of response (improvement) to therapy.

Reassessment is recommended after every intervention, large or small. This will detect the status of the patient upon which further intervention can be done. Frequently, assessment and monitoring may be required on a continuous basis.

1. Noninvasive monitoring

Frequent evaluation of clinical signs is the best way to monitor. There are mainly five clinical signs of cardiac output or perfusion:

- i. Heart Rate (HR) [tachycardia or bradycardia] and pulse [bounding or weak]
- ii. Altered mental status
- iii. Blood Pressure (BP) [hypotension]
- iv. Capillary refill [flash or prolonged]
- v. Urine output [< 1 ml/kg]

Signs of fluid overload or pulmonary edema need to be evaluated after every fluid bolus:

- i. Hepatomegaly
- ii. Cardiac gallop / Rales / JVD
- iii. Increased work of breathing and decreasing arterial oxygen saturation

2. Advanced monitoring

Bedside clinical signs of physiologic status are the basis of monitoring in resource limited settings. However, advanced and invasive monitoring is recommended in facilities that have such capabilities.

- i. Serial serum lactate measurement
- ii. Central venous pressure (CVP)
- iii. Continuous invasive arterial blood pressure monitoring
- iv. Mixed venous saturation, SVO_2 (goal > 70%)

v. Pulmonary edema on chest radiograph

 $vi. \ \ Bedside \ ultrasound \ / \ echocardiography$

a. Fluid unresponsive state: full inferior venacava with lack of variation across respiratory cycle suggests that additional volume may not improve shock.¹³

b. Change in cardiac index (CI) with passive leg raising can predict fluid responsiveness.¹⁴

c. Myocardial dysfunction due to sepsis can be identified by serial echocardiography. Administration of inotropes (adrenaline) results in shock reversal in the presence of ventricular dysfunction.¹⁵

d. Therapy should be directed towards achieving normal stroke volume and systolic function [Goal: CI 3.5 - 5.5 L/min/m², stroke volume index (SI) 30 - 60 ml/m², systemic vascular resistance index (SVRI) 300 - 1600 dyne-s/cm5/m2].⁴

Source control and antimicrobial therapy

1. Source Control: Recognition of the cause of the infection is of utmost importance and immediate attempt to remove the source of infection is required to prevent spread and decrease systemic inflammation. This may be in the form of drainage of abscess or empyema, debridement of necrotic tissue, or removal of hardware. Attempt at stabilisation of patient and source control need to be conducted simultaneously. In other words, source control should not be delayed.

2. Antibiotics: Immediate collection of samples for blood culture, urine culture or any other culture according to presumed source of infection is recommended. Antibiotics need to be administered within the first hour, if shock is present and after the cultures are drawn, if possible. If sepsis is suspected, without evidence of shock, antibiotics may be delayed for up to three hours to obtain further information regarding reason for sepsis.⁴ Every attempt should be made to identify the source of infection and treat with appropriate antibiotics. Recommendations for antibiotics are discussed in a separate article in subsequent issue of this journal by the same group under NEPAS protocols.

Treatment

1. Oxygen supplementation

i. Noninvasive

The panel recommends oxygen supplementation for all children with fluid refractory septic shock.

a. Face mask with 6 - 10 L/minute of oxygen flow may be used.

b. Non-rebreather masks utilising 15 L/minute of oxygen flow may be needed for children presenting with lower oxygen saturation.

c. More support can be provided by specialised Hi-Flo nasal cannula (HFNC) at 1 - 2 L/kg of flow (maximum flow: 30 L < 10 years, 60 L > 10 years)

d. Noninvasive positive pressure ventilation (NPPV) in the form of continuous (CPAP), starting at a pressure of 5 cm H_2O , or bilevel (BiPAP), starting at pressure support of eight and CPAP of 5 cm of H_2O , may be initiated.

ii. Invasive

Endotracheal intubation and invasive ventilation depend on the level of shock and resource availability.

a. In a facility where there is a lack of trained manpower and resources, intubation may be even more detrimental to the patient. In such a situation endotracheal intubation is only recommended in the event of impending respiratory arrest and immediate transport to a higher centre is essential.⁴ Support and oxygen may be provided via noninvasive positive pressure ventilation or Hi-Flo nasal cannula if patient requires vasoactive or inotropic support.

b. In a higher level of PICU, endotracheal intubation and mechanical ventilation could be provided in the event of fluid and vasoactive / inotropic refractory shock or impending respiratory failure / myocardial dysfunction.

Drugs for intubation: Ketamine can be used to sedate a child for intubation. Drugs that can cause myocardial depression and hypotension (benzodiazepines, propofol) and adrenal suppression (etomidate) should be avoided. Fentanyl may be used with careful monitoring. Lung protective ventilation with high positive end expiratory pressure (PEEP), low tidal volume, and low supplemental oxygen (FiO₂) is recommended for invasive mechanical ventilation. Avoiding auto PEEP and maintaining plateau pressure below 30 cm H_2O can further protect lungs. It is recommended to accept mild hypoxemia and hypercarbia if necessary. Prone positioning can help with oxygenation.

2. Fluids

i. Maintenance fluid:

Children presenting with sepsis including suspected or confirmed infection and hypothermia or hyperthermia but are normotensive may be administered maintenance IV fluid.⁴ Avoid fluid boluses.⁷ Careful monitoring of signs of decreased cardiac output and hypotension is essential.

Type of fluid: Normal saline (NS) or lactated ringers (LR). Add dextrose if serum glucose is below 150 mg/dL.

ii. Fluid bolus:

Children presenting in shock (Table 1) should be administered fluid bolus.^{4,7}

Type and amount of fluid: 10 - 20 ml/kg aliquots of normal saline or lactated ringers are administered up to 40 - 60 ml/kg over the first two hours. Careful reassessment of cardiac output / perfusion is necessary after every bolus. Fluid is discontinued immediately if signs of fluid overload develop. Particular monitoring and slow fluid infusion (10 -15 ml/kg in one hour) are required in children admitted with severe malnutrition and shock.⁷

3. Blood products

i. Cross matched packed red blood cells (PRBC), 10 ml/kg may be administered in children with haemoglobin of less than 6 g/dL after two fluid boluses and still hypotensive^{3,7} but have no signs of fluid overload (Table 3). Slow blood transfusion is recommended in haemodynamically stable patients only if haemoglobin falls below 4 g/dL.^{3,7}

ii. Platelets transfusion of 10 ml/kg is only recommended when the level falls below 10 - 20,000/mm³ if patient is not bleeding, or below 50,000 if patient shows some evidence of bleeding.

Guidance for Management of Sepsis and Septic Shock; Basnet S et al.

iii. Fresh frozen plasma (FFP) is not routinely administered in children with septic shock without evidence of bleeding.

4. Vasoactive Medications

i. If more fluid (after a total of 40 - 60 ml/kg) does not improve the perfusion status of the patient or signs of fluid overload and pulmonary edema develop, vasoactive medications need to be initiated.

ii. Initially: Adrenaline or noradrenaline can be used for septic shock administered centrally (peripherally for short periods of time if central line is not available).⁴ Dopamine may be administered if adrenaline and noradrenaline are not available.

a. Dose: Adrenaline or noradrenaline is infused at starting dose of 0.05 mcg/kg/min and titrated up to 1 mcg/kg/min

b. Dopamine can be started at 5 mcg/kg/min and titrated up to 20 mcg/kg/min.

iii. Whichever infusion is initially started, if it reaches 0.1 mcg/kg/min, the second infusion may need to be initiated to improve patient status.

iv. Subsequent management: Recent guidelines ⁴ recommend using advanced haemodynamic monitoring including ultrasound Doppler / echocardiogram to determine further resuscitation of children with fluid refractory septic shock. However, majority of facilities in Nepal lack these advanced techniques. Therefore, cold shock (low CI and high SVRI) and warm shock (high CI and low SVRI), and further therapy with either adrenaline or noradrenaline, may still need to be differentiated using clinical variables.⁵

a. Adrenaline (inotrope) is titrated up if cold shock is suspected (hypotension, thready pulse, cool extremities and delayed capillary refill with narrow pulse pressure).

b. Noradrenaline (vasopressor) is titrated up for warm shock (hypotension with bounding pulse, flash capillary refill and wide pulse pressurelow diastolic pressures).

v. Inodilators such as dobutamine or milrinone may need to be added only if blood pressure is high normal yet other signs of decreased perfusion persist.

5. Corticosteroids

IV hydrocortisone (1 - 2 mg/kg every six hours) may be administered if hypotension and decreased perfusion persist even after adequate fluid and vasopressor / inotropic therapy. It should not be initiated until these therapies have been maximised.

6. Calcium, glucose, antipyretics

Maintain normal serum calcium. Calcium replacement with calcium gluconate is recommended if ionised serum calcium is low. Dextrose is added to maintenance fluid once serum glucose is 150 mg/dL (7.8 mmol/L) or lower. Paracetamol is administered for oral or rectal temperature over 101°F.

7. Nutrition

Nutrition needs to be provided to the patient via oral or gastric / postpyloric feeding tube. Feeding should be started as early as possible, once patient is hemodynamically stable.

8. Fluid overload

Fluid overload needs to be avoided with judicious use of fluid boluses and careful monitoring and reassessments. However, if it does develop post resuscitation, diuretics may be used to remove excess fluid. Furosemide bolus or infusion started at low dose and titrated up based on urine output will decrease extra body water.

CONCLUSIONS

This clinical guidance for management of sepsis and septic shock in children in Nepal is a consensus document, keeping in view the resources available, created by paediatricians working in various PICUs in the country and based / adapted from the Surviving Sepsis Campaign 2020. This is an attempt to decrease variability in critical care delivery and standardise care by providing a guide to providers. Use and efficacy of this guideline will be monitored after dissemination and implementation.

APPENDIX 1: SEPSIS AND SEPTIC SHOCK MANAGEMENT PROTOCOL

STEP 1: 0 – 5 min. Recognise decreased perfusion / call for help

- Oxygen by non-rebreathing mask 15 L/min (use facemask 6 10 L/min if not available)
- Noninvasive ventilation (HFNC / NPPV) if increased WOB
- Bag mask ventilation, and prepare for intubation if unstable airway / bradypnea / apnea / gasping

STEP 2: 0 - 60 min. IV Access 3 attempts [if unable place IO]

- Send blood/urine samples for tests [Labs]
- If normotensive, start maintenance fluid
- If hypotensive (see box) 1st Bolus: NS or LR 10 20 mL/kg over 30 minutes
- [Check for signs of fluid overload: ONLY 10 ml/kg slow if suspicion of cardiac congestion or severe malnutrition]
- First dose antibiotics [after blood cultures]
- If still hypotensive, 2nd bolus: NS or LR 10 20 mL/ kg over 15 30 minutes [Total 40 ml per kg]
- Correct hypoglycemia
- Place urine catheter
- If still hypotensive and Haemoglobin < 6 g/dL, consider PRBC transfusion at 10 ml/kg

Hypotension:

• Low systolic BP (see Table 2) **OR**

• All three of following: cold extremities, capillary refill > 3s, weak fast pulse

AND

• Decreased Urine Output and/or altered mental status

REASSESS:

- 1. Signs of decreased perfusion: Tachycardia, abnormal capillary refill, oliguria / anuria, altered mental status, hypotension
- Fluid Overload: Work of Breathing (WOB), increasing RR, hepatomegaly, PE / rales / cardiac gallop / JVD

Labs: CBC, Metabolic screen [Na, K, Calcium (ionised if possible)], albumin, BUN, Cr], liver function test, coagulation profile, blood C/S, urine RME and C/S, dextrose stix (RBS), CRP, and blood gas (if available), lactate (if available), blood group, disease specific serology.

REASSESS (see box) frequently and / or after each bolus for signs of decreased perfusion, hypotension and / or fluid overload)

Shock resolved: improved HR, Cap refill < 2 seconds, normal BP, good urine output / mental status. No hepatomegaly / cardiac gallop / rales Shock NOT resolved: Arrange for PICU /Referral to tertiary center, No Hepatomegaly and / or cardiac gallop /Pulmonary edema/rales *Shock NOT resolved*: Arrange for PICU / Referral to tertiary center **Presence of** Hepatomegaly / cardiac gallop /pulmonary edema / rales

Continue monitoring

FLUID REFRACTORY

Stop fluid bolus. Start epinephrine 0.05 mcg / kg/min

FLUID REFRACTORY SHOCK

STEP 3 Start inotrope/vasoconstrictor (may infuse via peripheral line for short period until central line is placed) at 0.05 mcg/kg/min REASSESS continuously and titrate [see box]

And <u>whenever possible</u> CVP, invasive arterial BP, ScVO₂ [goal >70%], CI [3.3 - 5.5L/min/m²], SI [30 - 60 mL/m²], SVRI [800 - 1600 dynes-s/cm⁵/m²]

Further management: depends on signs of myocardial dysfunction OR decreased systemic vascular resistance (SVR)

COLD SHOCK (or evidence of myocardial dysfunction) Hypotension, thready pulse, cool extremities, delayed cap refill, low pulse pressure (< 20 mm Hg), low CI

WARM SHOCK (or evidence of decreased SVR)

Hypotension, bounding pulse, flash cap refill, wide pulse pressure (target pulse pressure 40 mm Hg); normal / high CI REASSESS:

 Signs of decreased perfusion: Tachycardia, abnormal capillary refill, oliguria / anuria, altered mental status, Hypotension

2. Fluid Overload: Work of Breathing (WOB), increasing RR, hepatomegaly, PE /rales / cardiac gallop / JVD

Use USG if available, to direct fluid, inotrope, vasopressors, vasodilators

> REASSESS every 5 minutes

EPINEPHRINE

May titrate up to 1 mcg/kg/min

NOREPINEPHRINE

May titrate up to 1 mcg/kg/min

Consider Dopamine as the first-line vasoactive infusion if epinephrine or norepinephrine are not readily available.

Consider adding Norepinephrine once epinephrine is 0.1 mcg/kg/min

Consider adding Epinephrine or Vasopressin once Norepinephrine is 0.1 mcg/kg/min

IF BP NORMAL OR HIGH but signs of decreased perfusion present, Consider **Dobutamine (5 mcg/kg/min) [or milrinone** 0.25 mcg/kg/min]

May continue judicious fluid boluses if fluid responsive and NO signs of fluid overload.

Shock NOT resolved [PRESSOR/INOTROPE RESSISTANT SHOCK]

HYDROCORTISONE 1 - 2 mg/kg every 6 hours [or 50 mg/m²] Administer earlier if suspicion of adrenal suppression

Consider administering **IV Calcium at any time** if low serum calcium / low ionised Calcium Calcium gluconate 100 - 200 mg/kg (max. 10 ml, dilute in equal volume of NS) [Do not administer in same line as pressors / inotropes]

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