

Randomized controlled trial of interventions for treatment of shock in children with severe acute malnutrition and cholera or other dehydrating diarrheas

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What is Sepsis?

Sepsis is defined as life-threatening organ dysfunction caused by dysregulated host response to infection

At least 2 of the following in association with an infection:

- Hypo or hyperthermia
- Hurried respiration
- Leucopenia or leucocytosis
- Immature neutrophils

Paediatric

The Newcastle upon Tyne Hospitals 
NHS Foundation Trust

RED FLAGS... THINK SEPSIS!

Suspected or proven infection AND has 1 of the following:



Core temperature



Hypoxemia



Inappropriate tachycardia
see PEWS chart



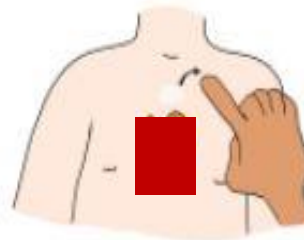
Have a lower threshold of suspicion for:

Patients younger than 3 months,
chronic disease, recent surgery,
immunocompromised



Altered mental state

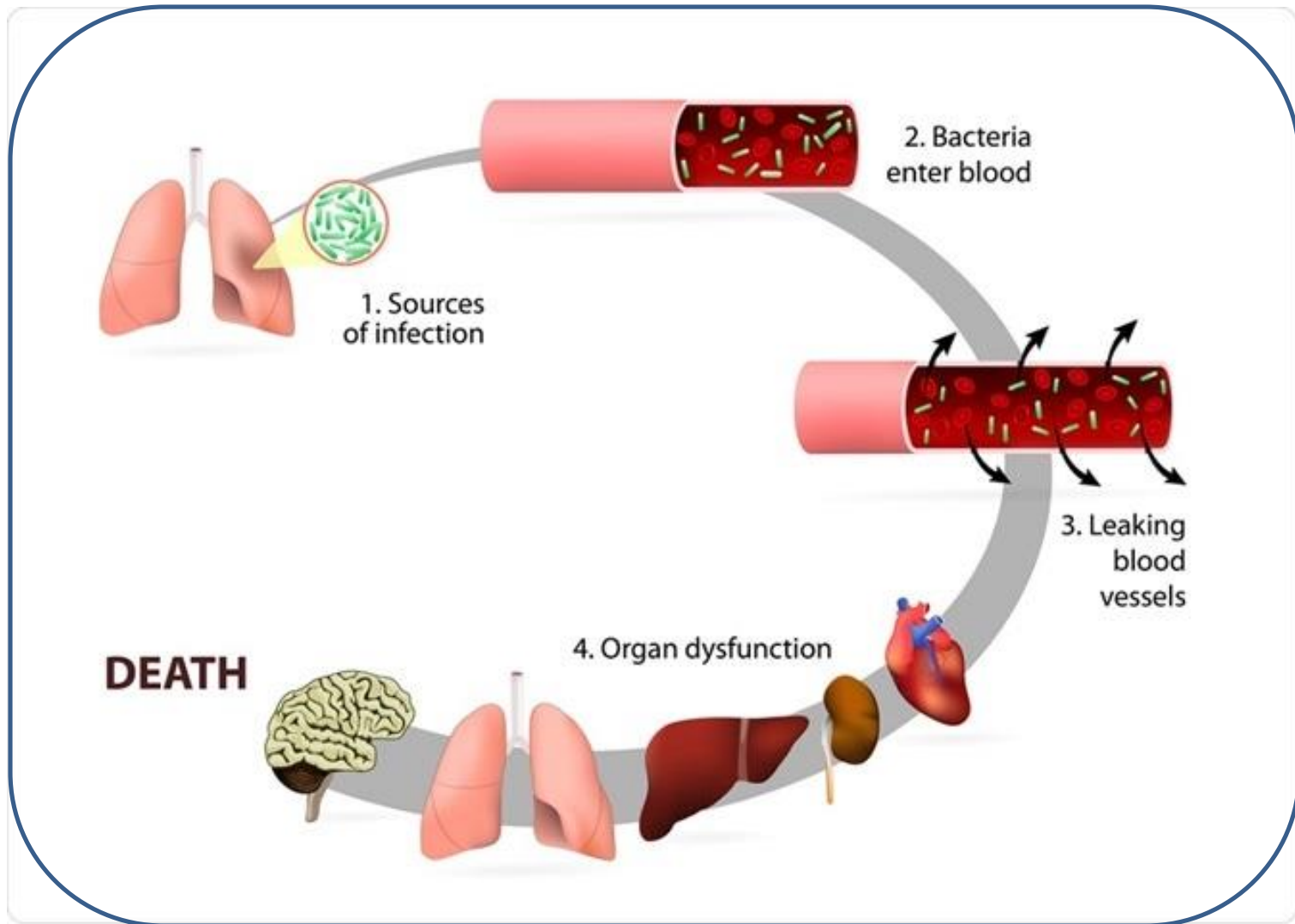
Inc., sleepiness, irritability, lethargy,
floppiness



prolonged capillary refill
(reduced skin perfusion)



Suspect sepsis. Say sepsis. Save someone's life today

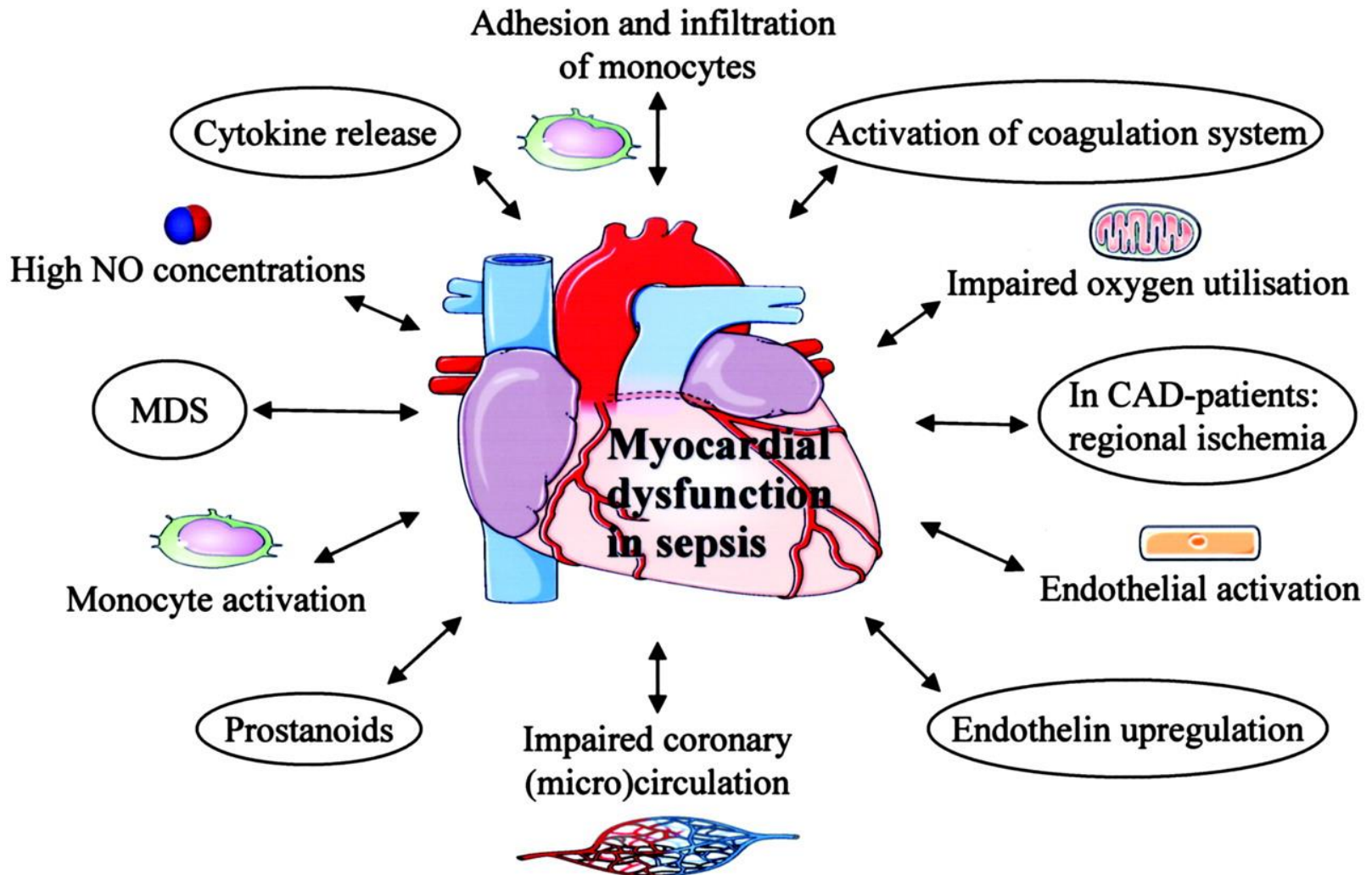


What is Shock?

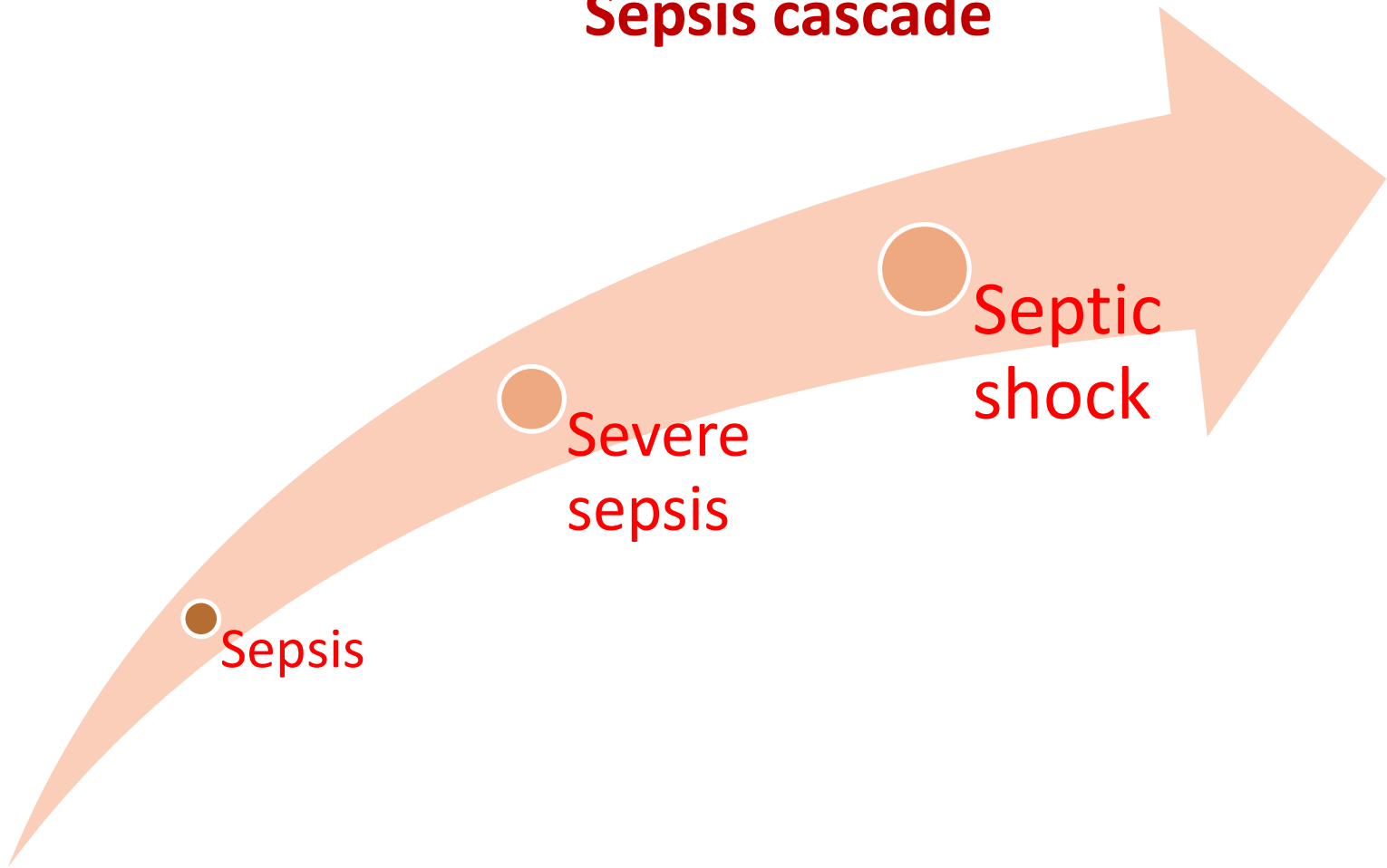
Shock is a state characterized by a significant, systemic reduction in tissue perfusion, resulting in decreased tissue oxygen delivery and diminished removal of harmful byproducts of metabolism (eg. lactate)

Septic shock is sepsis-induced hypotension (MAP < 50 mm Hg in children / < 65 mm Hg in adults) persisting despite adequate fluid resuscitation

The heart is affected by sepsis, septic shock



Sepsis cascade



RESEARCH ARTICLE

Severe Sepsis in Severely Malnourished Young Bangladeshi Children with Pneumonia: A Retrospective Case Control Study

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- The management of severe sepsis in SAM included fluid resuscitation (20 ml/kg per hour; max 40 ml over 2 hours) following standard protocol of the Dhaka hospital of icddr,b (Ahmed T et al. The Lancet, 1999)
- The mortality in severe sepsis was only 4%, but 40% among those who developed septic shock
- The evidence of fluid overload and heart failure during this period was low (<3%)

Predictor of Death in Diarrheal Children Under 5 Years of Age Having Severe Sepsis in an Urban Critical Care Ward in Bangladesh

Sarmin M, Afroze F, Zaman S, Alam T, Shaly N, Ahmed T, Chisti M

Global Pediatr Health 2019

Variable	Odds Ratio	95% Confidence Interval	P
Shortness of breath	3.56	1.39-9.12	<.01
Abnormally sleepy	2.94	0.82-10.49	.10
Dehydrating diarrhea	0.33	0.12-0.89	.02
Septic shock	29.70	8.12-108.62	<.01

The ICU of the Dhaka hospital of icddr,b manages around 1000 pediatric patients each year. Around one-fourth of them have severe sepsis/septic shock, one-third have SAM and more than half of them are admitted with severe pneumonia. Overall death rate in ICU is 11%.

Among the children with severe sepsis/septic shock who are admitted in the ICU, more than half of them have severe malnutrition.

Case fatality rate is 40% and 69% in SAM children with severe sepsis and septic shock respectively. This means that case fatality rate was 69% in children with SAM unresponsive to crystalloid and/or blood transfusion that was given according to the recommendations

WHO criteria for shock in children with SAM

- delayed capillary refill time of more than 3 seconds
- weak and fast pulse
- cold extremities
- and reduced level of consciousness, i.e. lethargy or loss of consciousness

WHO recommendation for SAM with shock

IV fluids are recommended @ 15 ml/kg over 1 h

- Ringer's lactate with 5% glucose
- Half-strength Darrow's solution with 5% glucose
- 0.45% NaCl plus 5% glucose

WHO recommendation for SAM with shock

- Measure the pulse rate, volume and breathing rate at the start and every 10 min
- If there are signs of improvement (pulse rate falls by 15 beats/min, pulse volume increases or respiratory rate falls by 5/min) and no evidence of pulmonary edema
 - Repeat IV infusion at 15 ml/kg over 1 h; then
 - Switch to oral or NG rehydration at 10 ml/kg/hour

WHO recommendation for SAM with shock

If the child deteriorates during IV rehydration

- breathing increases by 15 breaths/min or
- pulse increases by 5 beats/min
- stop the infusion because IV fluid can worsen the child's condition

- If the child fails to improve after first 15 ml/kg
 - give maintenance IV fluid (4 ml/kg per h) while waiting for blood
 - when blood is available, transfuse @10 ml/kg slowly over 3 h



A child with SAM, diarrhea and septic shock: at extreme risk of death



A child with MAM, diarrhea and hypovolemic shock: recovery with proper IV fluid therapy

Rationale

- Case fatality high among children with SAM, shock
- WHO nutrition guidelines recommend blood transfusion to children with SAM and shock not responsive to IV fluids
- Evidence behind blood transfusion?
- Blood transfusion is not feasible in all places
- Dopamine is being used in some places to treat septic shock in children

General Objective

To evaluate the efficacy of WHO standard fluid therapy followed by dopamine compared to WHO standard fluid therapy followed by blood transfusion for the management of shock in children with SAM and cholera or other dehydrating diarrheas

Specific Objectives

Among children with SAM, dehydrating diarrhea and shock to:

- identify the treatment failure rates
- calculate the recovery time of the study patients
- calculate the duration of ICU stay as well as total period of hospitalization
- identify the patients who need mechanical ventilation
- evaluate the incidence of heart failure during hospitalization
- evaluate cardiac function at enrollment

Study design

- Randomized, two-arm, controlled, non-masked clinical trial in children 1-59 months old with SAM and shock
- The arms will have blood transfusion & dopamine
- The trial will be conducted at the ICU of icddr,b Dhaka Hospital
- Ethics approval will be obtained from the icddrb IRB
- Parents will be properly explained and the children will be enrolled only upon obtaining informed written consent

Inclusion criteria

- Children of both sex, aged 1-59 months, with diarrhea and SAM and shock
- SAM: A child with a <-3 Z-score of weight for height/length of the median value of the WHO standard or MUAC <115 mm (for children >6 months of age), or presence of nutritional edema
- In addition to the WHO definition of shock, BP will also be recorded and monitored
- $MAP = (Systolic + Diastolic \times 2) \div 3$

Exclusion criteria

- Children with severe anemia, Hgb <5 g/dl
- Congenital anomalies
- Trisomy 21
- Any pre-existing morbidity

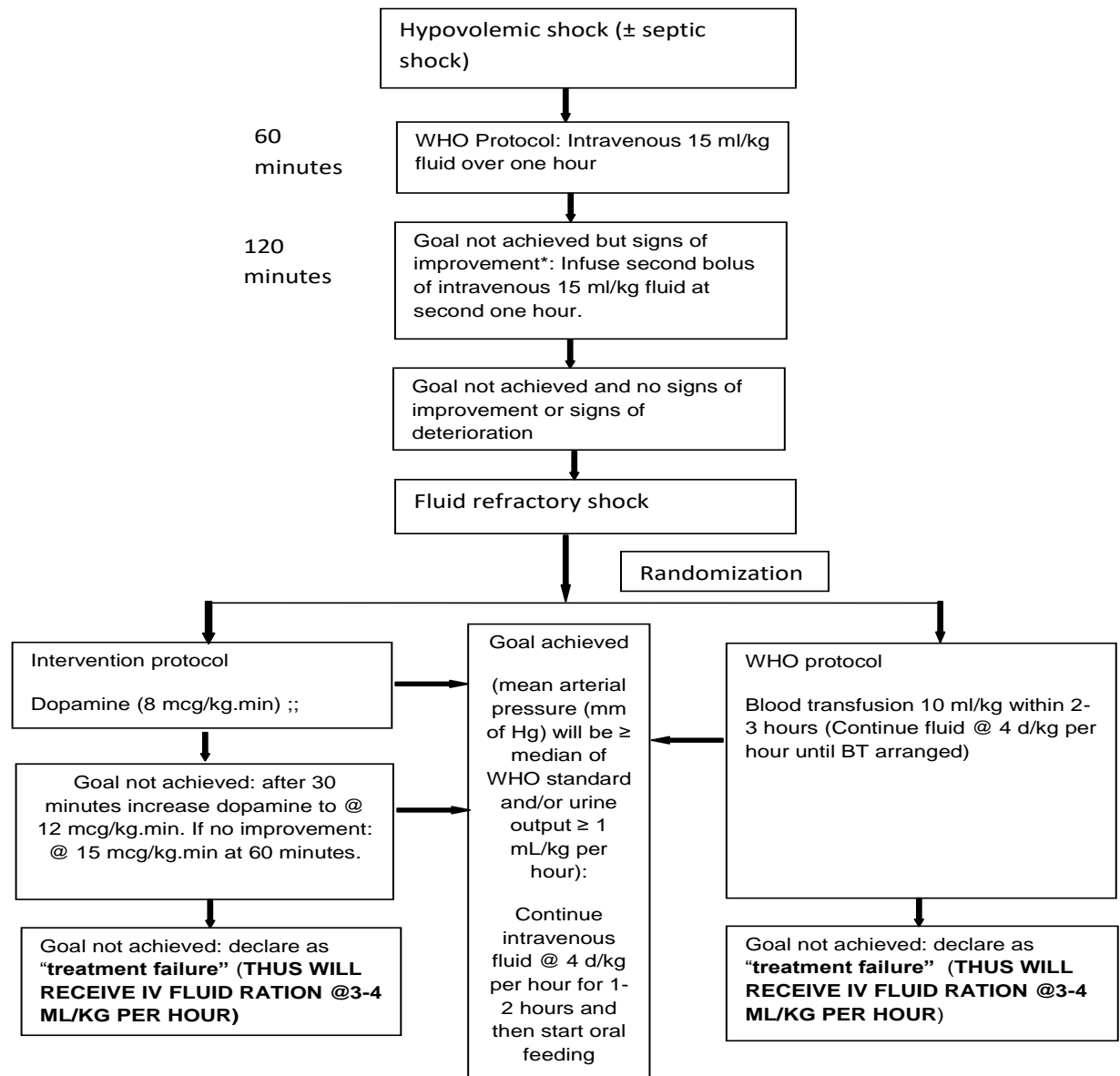
Clinical management

- Treatment in the ICU
- Customized, pre-tested case record form will be used
- Study staff will monitor progress jointly with ICU staff
- Oxygen saturation, blood biochemistry, blood/stool urine cultures will be performed
- Procalcitonin, troponin I will be measured on enrolment
- CSF study, radiology performed as and when required
- Antimicrobial therapy, feeding will be done as per standard protocol

Clinical management

- Cardiac USG will be performed at admission to evaluate cardiac structure and function
- After the acute phase treatment is over, children will be kept in the NRU for nutritional rehabilitation

Figure 1: Flowchart of the proposed and WHO standard intervention



Rescue therapy with Adrenaline?

*Signs of improvement: Pulse rate falls, pulse volume increase, or respiratory rate falls and no signs of pulmonary edema. #Signs of deterioration: breathing rate increases by 5/minute, pulse rate increases by 15/minute, liver enlarges, fine crackles throughout the lung fields, jugular venous pressure increases, galloping heart rhythm develops.

All study children will receive antibiotics, oxygen, monitoring and feeding as per Dhaka hospital protocols

Treatment failure

Treatment failure will be defined if an intervention results in MAP < 50 mm of Hg or diastolic pressure < 40 mm of Hg and/or urine output is < 1 ml/kg per hour 180 minutes after the intervention

Sample size

2010-11 data from our ICU revealed that among the 36 severely malnourished children with shock, 22 died i.e. mortality rate among SAM children with shock was 61%

We assume that the proposed interventions would reduce the case fatality rate by 50%, i.e. the rate will decrease from 61% to 31%. To detect this magnitude of difference in the death rate, with 80% power and 0.05 type I error, the required sample size is 40 children in each of the two groups.

Considering 10% dropouts, the total sample size would be 45 children at least in each of the two groups. However, we can even go beyond 45 if recruitment period allows.