Sepsis

for pediatric residents

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Response to infection

- **Normal :** localized, controlled inflammation→ localize and control microbial invasion

- **SIRS(systemic inflammatory response syndrome)- triggering agent where not adequately recognized and cleared:** excessive, generalized, uncontrolled release of inflammatory mediators→ vasodilation, ↑vascular permeability, ↑ vascular damage→ **inadequate circulation to tissues(shock)**

Septic shock

Combination of :

- Hypovolemic shock: intravascular fluid loss through capillary leak
- Cardiogenic: myocardial depressant effect of sepsis
- Distributive: decreased systemic vascular resistance

Compensatory mechanisms

- Sympathetic nervous activation, hormonal response(epinephrine-norepinephrine):
  - ↑HR –
  - ↑ Contractility –
  - ↑ Peripheral vaso-constriction –
- Respiratory compensation:
  - ↑ RR: eliminate Co2, compensate acidosis –
- Renal compensation: eliminate hydrogen ions, retention of bicarbonate

Decompensated shock

- ↓BP
- MODS(Multisystem organ dysfunction syndrom): **any alteration of organ function that requires medical support for maintenance**

MODS: any alteration of organ function that requires medical support for maintenance

- Circulation: Shock, oliguria, metabolic acidosis, ↑ CRT
- Lung: ARDS(PaO2/FiO2 <300), FiO2> 50 for O2 saturation ≥92% , PaCO2 >65
- Liver: ↑ LFT> 2 times of NL, bilirubin> 4mg/dl
- Kidneys: ↑ Cr ≥2 times of normal or twofold increase in baseline
- Brain: GCS< 11, or acute change in mental status
- Hematologic: Plt< 80,000 or decline of 50% from past 3 d value, DIC

Signs of low perfusion

Organ system	↓ perfosion	↓↓ perfosion	↓↓↓ perfosion
CNS		Restless, apathetic, anxious	Agitated, confused, stupourus, coma
Respiration		↑ RR	↑↑ RR
Metabolism		Compensated metabolic acidosis	Uncompensated metabolic acidosis
Kidney	↓ urine volume ↑ urine SG	Oliguria	Oliguria/ anuria
Skin	↑ CRT	Cool extremities	Mottled, cyanotic, cool extremities
Cardiovascular	↑ HR	↑↑ HR, ↓ peripheral pulses	↑↑ HR, ↓ BP, central pulse only

Systemic inflammatory response syndrome= pre-shock due to severe inflammation

- Core(rectal, oral) *T*> 38.5 or <36
- Unexplained *HR*> 2SD or < 10% in less than 1 yr
- Unexplained *RR*> 2SD or need to MV
- Unexplained *WBC*> 12000 or < 4000 or *band* cell> 10%

➢ Abnormal temperature (fever or hypothermia) or WBC count + one of the following: tachycardia, bradycardia, respiratory distress, or need to mechanical ventilation

HR> 2SD

(American College of Critical Care Medicine)

- < 1 yr.: > 180/min
- 1-5 yr: 140/min
- 5-12 yr: 130/min
- > 12 yr: 110/min

- Each 1 ^{o}C increase in temperature increase heart rate by 10/min
- Tachycardia may be due to fever, anxiety, dehydration, pain/discomfort, anemia, or agitation

HR> 2SD

(AAP, Pediatric Advanced Life Support)

- < 3 mo.: 250
- 3 mo. – 2 yr. : 190
- 2-10 yr. : 140
- > 10 yr.: 100

RR> 2SD

- < 2mo: > 60/min
- 2-12 mo: > 50/min
- 1-5 yr: > 40/min
- 6-8 yr: > 30/min
- > 8 yr: > 20/min

➢ Each ^{o}C increase in temperature increase respiratory rate by 4-10/min

Hypotension(SBP)

- < 1 mo: <60 mmHg
- 1 mo- 10 yr: <70+ 2 age(yr)
- > 12 yr: < 90 mmHg

Stages of septic shock

- Early(Warm): ↑↑↑ CO, ↓↓↓ SVR:
  - Flash capillary refill (<1 second)
  - Bounding pulses
  - Warm, dry extremities
  - Wide pulse pressure (> 40 mmHg, lower in infants)
- Late: ↓↓ CO, ↓↓ SVR:
  - Delayed capillary refill (>2 seconds)
  - Diminished pulses
  - Mottled or cool extremities

WHO definition of shock
(requires bolus fluid)

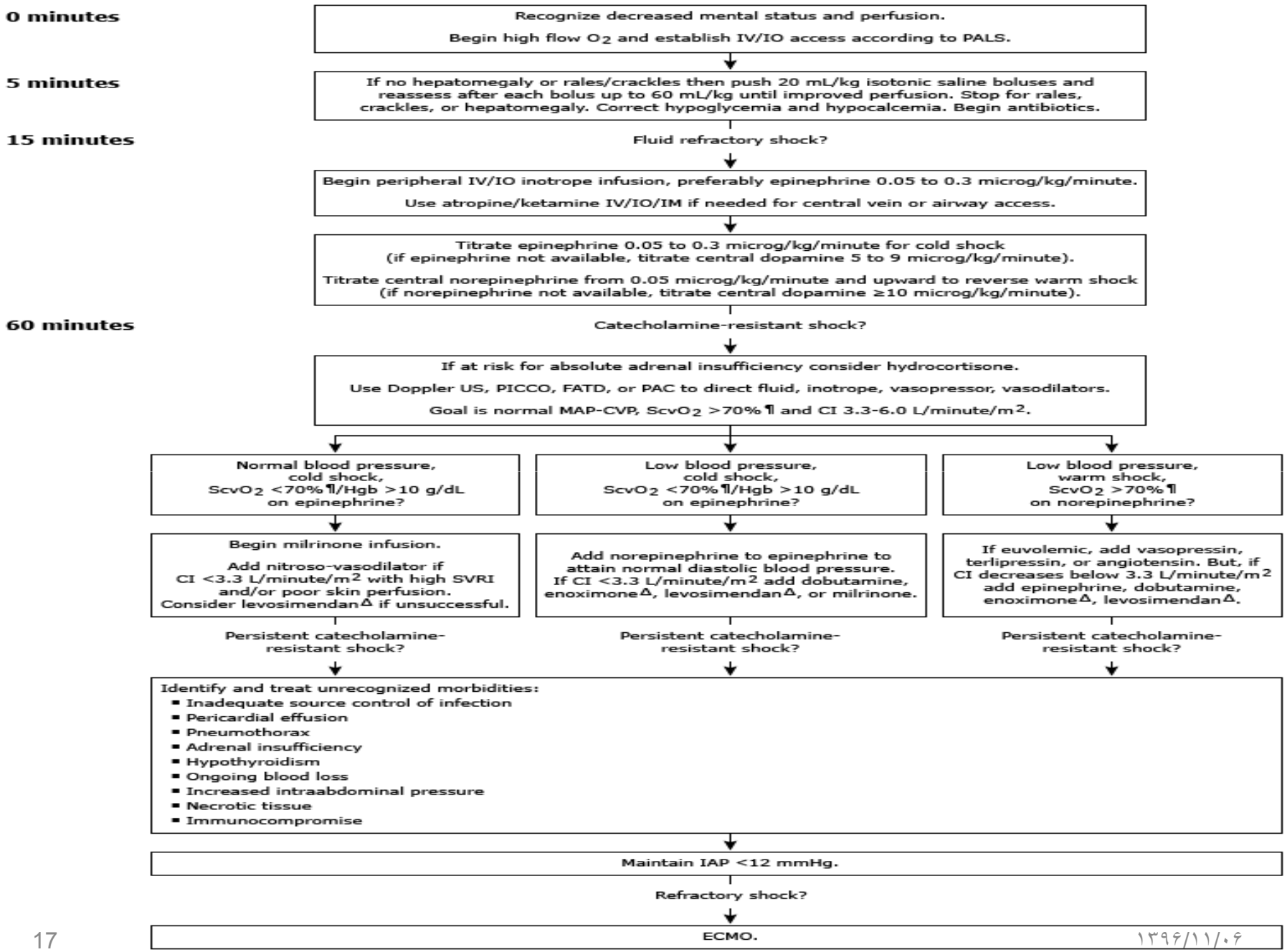
- Cold hands
- CRT> 3 sec
- Fast and weak pulses

Definitions

- **SIRS**: severe inflammatory pre-shock
- **Sepsis**: pre-shock due to infection
- **Septic shock:** Sepsis+ despite 40cc/kg of isotonic fluid
  - ↓ BP or need to vasoactive drug to maintain BP
  - 2 of: oliguria, metabolic acidosis, ↑↑ CRT, ↑ lactate
- **Fluid-refractory septic shock:** shock despite 60 mL/kg of fluid resuscitation
- **Catecholamine-resistant septic shock:** shock despite dopamine ≥10 mcg/kg/min and/or direct-acting catecholamines (epinephrine, norepinephrine)
- **Severe sepsis**: sepsis +
  - Shock
  - ARDS
  - 2 organ dysfunction
  - MODS

Etiology

- Staphylococcus aureus
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Enterococcus species
- Meningococcal infections
- Enteric Gam negatives: Pseudomonas aeruginosa, Escherichia coli, Klebsiella species
- Alpha streptococcus in AML and neutropenia
- Coagulase-negative Staphylococcus especially in neonates or In-dwelling vascular catheters
- Group B streptococcus in the neonate


0 minutes
Recognize decreased mental status and perfusion.
Begin high flow O_2 and establish IV/IO access according to PALS.
5 minutes
If no hepatomegaly or rales/crackles then push 20 mL/kg isotonic saline boluses and reassess after each bolus up to 60 mL/kg until improved perfusion. Stop for rales, crackles, or hepatomegaly. Correct hypoglycemia and hypocalcemia. Begin antibiotics.
15 minutes
Fluid refractory shock?
Begin peripheral IV/IO inotrope infusion, preferably epinephrine 0.05 to 0.3 microg/kg/minute.
Use atropine/ketamine IV/IO/IM if needed for central vein or airway access.
Titrate epinephrine 0.05 to 0.3 microg/kg/minute for cold shock (if epinephrine not available, titrate central dopamine 5 to 9 microg/kg/minute).
Titrate central norepinephrine from 0.05 microg/kg/minute and upward to reverse warm shock (if norepinephrine not available, titrate central dopamine ≥10 microg/kg/minute).
60 minutes
Catecholamine-resistant shock?
If at risk for absolute adrenal insufficiency consider hydrocortisone.
Use Doppler US, PICCO, FATD, or PAC to direct fluid, inotrope, vasopressor, vasodilators.
Goal is normal MAP-CVP, $ScvO_2$ >70%¶ and CI 3.3-6.0 L/minute/m^2.
Normal blood pressure, cold shock, $ScvO_2$ <70%¶/Hgb >10 g/dL on epinephrine?
Low blood pressure, cold shock, $ScvO_2$ <70%¶/Hgb >10 g/dL on epinephrine?
Low blood pressure, warm shock, $ScvO_2$ >70%¶ on norepinephrine?
Begin milrinone infusion.
Add nitroso-vasodilator if CI <3.3 L/minute/m^2 with high SVRI and/or poor skin perfusion.
Consider levosimendan$^{\Delta}$ if unsuccessful.
Add norepinephrine to epinephrine to attain normal diastolic blood pressure.
If CI <3.3 L/minute/m^2 add dobutamine, enoximone$^{\Delta}$, levosimendan$^{\Delta}$, or milrinone.
If euvolemic, add vasopressin, terlipressin, or angiotensin. But, if CI decreases below 3.3 L/minute/m^2 add epinephrine, dobutamine, enoximone$^{\Delta}$, levosimendan$^{\Delta}$.
Persistent catecholamine-resistant shock?
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Persistent catecholamine-resistant shock?
Identify and treat unrecognized morbidities:
▪ Inadequate source control of infection
▪ Pericardial effusion
▪ Pneumothorax
▪ Adrenal insufficiency
▪ Hypothyroidism
▪ Ongoing blood loss
▪ Increased intraabdominal pressure
▪ Necrotic tissue
▪ Immunocompromise
Maintain IAP <12 mmHg.
Refractory shock?
ECMO.

1st hour

- Goals : restore or maintain
  - Airway, oxygenation, and ventilation
  - Circulation
  - Threshold heart rate
- Actions:
  - IV or IO access within 5 min preferably 2 sites and largest caliber
  - Fluid resuscitation within 30 min.
  - Antibiotics within 60 min.
  - For fluid-refractory shock, inotropic infusion within 60 min.

1st hour

- Initially 100% supplemental oxygen, once perfusion restored avoid SpO2 >97%
- Fluid resuscitation: 20 mL/kg of NS or lactated Ringer solution over 5 min. with a "push-pull" technique or rapid infuser
- Assessment for signs of inadequate and overload (eg, pulmonary rales or gallop rhythm) before and after each bolus
- Up to 60 mL/kg in the 1st hr. and to 120 mL/kg or more during the several hrs.

1st hour

- Rapid fluid infusion in resource-limited settings should be avoided
- Crystalloid solution instead of albumin because of the lack of clear benefit and higher cost
- Albumin if no improve following >60 mL/kg of fluid, albumin <3 g/dL, or hyperchloremic metabolic acidosis
- Correction of hypocalcemia and hypoglycemia
- If obtaining BC is difficult, not impede antibiotic initiation within the first hour

Empiric AB regimens

- Ceftriaxone+ vancomycin: most children:
- Meropenem or tazocine instead of ceftriaxone if GUor GI sources (eg, UTI appendicitis), or immunosuppressed
- Add clindamycine or metrondazol for possible GI source
- Add ampicillin in age ≤28 d.

Therapeutic endpoints for reversal of shock

- Strong and equal central and peripheral pulses
- Skin perfusion (warm, with CRT<2 seconds)
- Normal mental status
- U/O (≥1 mL/kg/hour, up to 40 mL/hour)
- BP
- Normal serum lactate (eg, <2 mmol/L)
- ScvO2 ≥70%
  - Specific goal for HR is difficult to define and may not be useful.

Goal directed aggressive fluid therapy

- Push 20 mL/kg N/S or ringer lactate (if no hyperkalemia) each 5-15 minute
- Up to 60/kg in 1st hours, sometimes as much as 120 mL/kg or more in several days
- Albumin after 60 cc/kg fluid therapy
- Other coloids if needed(↑PT & PTT, ↓Hb)
- If cardiac problem exist 5-10 mL/kg fluid every 30-60 min with close monitoring

Early inotropic therapy

(after 40cc/kg fluid)

Initially peripheral lines with close monitoring of IV line, then central line

- Cold shock:
  - **Epinephrine**(0.05-1.5 microgram/kg/min) [0.6BW/100cc DW5%, 0.5-15 micro-drop /min]
  - If no improve and ↓BP: titrate norepinephrine, if ↓ CI add dobutamine
  - If no improve and NL BP: titrate milrinone
- Warm shock:
  - **Norepinephrine**(0.03-1.5 microgram/kg/min) [0.6BW/100cc DW5%, 0.5-15 micro-drop /min] in warm shock via perpheral IV lines
  - If no improve and euvolemic: add vasopressin
  - If no improve and ↓CI: titrate epinephrine/dobutamine

Stress dose corticosteroid therapy

- Should be give(at risk of adrenal dysfunction):
  - Congenital adrenal hyperplasia
  - Abnormality in hypothalamic- pituitary axis
  - Recent therapy(> 2 wk., > physiologic dose) with corticosteroid
  - Fluid and inotrope resistant shock
  - 2-4 mg/kg or 50 to 100 mg/m2/day hydrocortisone(up to 100 mg) with/without check of total random cortisol level

Catecholamine resistant shock

- Cold shock + ScVo2< 70% + NL BP:
  - Add milrinione infusion
  - If low CI + high SVR and/or low perfusion skin: add nitroglycerin infusion
- Cold shock +ScVo2< 70% + ⬇BP:
  - Add norepinephrine to normalize diastolic BP
  - If low CI : add dobutamine or milrinon infusion
- Warm shock +⬇BP:
  - If euvolemic: add vasopresin
  - If low CI: add epinephrine or dobutamine

Further management

- Assessment the source of the infection
- Assessment of organ dysfunctions
- Stress dose corticosteroid in resistant shock
- Supporting care for organ failure

Assessment the source of the infection

- CXR: pneumonia
- Gram stain and culture *of suspected infectious sites and petechia/purpura*
- B/C from two site simultaneously(bactec)
- U/A , U/C
- CSF *analysis and culture*

Assessment of organ dysfunction

- CBC diff: ↑ *or* ↓ *WBC,* ↓*plt,* ↓*Hb*
- ESR> 30, ↑CRP, ↑procalcitonin
- ↑PT, ↑PTT, ↑D-dimer, ↑FDP
- Blood lactate
- ABG or VBG: *Res. Alkalosis, Res. Alkalosis +Met. Acidosis, Mixed Acidosis, hypoxemia*
- LFT: ↑*AST,* ↑*ALT,* ↓*Alb,* ↑*Bil*
- ↑ *or* ↓ BS, ↓Ca, ↓Na , ↑TG
- ↑BUN, ↑Cr
- CXR: *ARDS, pneumonia*

Supportive care for organ dysfunction

Disorder	Goals (prevent/treat)	Therapies
ARDS	Hypoxia, respiratory acidosis	O_2
Respiratory muscle fatigue	Barotruma	Early intubation and MV
Central apnea	Decrease work of breathing	MV
Renal failure	Hypovo/hypervolemia, hyperkalemia, acidosis, hypo/hypernatremia, hypertension	Judicious fluid therapy Low dose dopamine, establish NL U/O and BP Lasix, dialysis
Coagulopathy(DIC)	Bleeding	Vit.K, FFP, PLT
Thrombosis	Abnormal clotting	Heparin, activated pr C

Supportive care for organ dysfunction

Disorder	Goals (prevent/treat)	Therapies
Stress ulcer	Gastric bleeding, aspiration, distension	H_2 blocker, PPI, Fix NG tube
Ileus, bacterial translocation	Mucosal athrophy	Early enteral feeding
Adrenal insufficiency	Adrenal crisis	Stress dose, physiologic dose
Metabolic acidosis	Correct etiology, normal PH	Treatment of hypovolemia, cardiac dysfunction, renal excretion, bicarbonate if PH< 7.1 and adequate ventilation

0-5 min

- High flow O_2
- Suctioning, ventilation if needed
- Establish IV/IO access

5-15 min

- Push 20 cc/kg NS and over 60 cc/kg until
  - Perfusion improved(Pulses,BP, CRT, U/O, MS, serum lactate)
  - Rales
  - Hepatomegaly
- Check BS and correct hypoglycemia
- Send lab exams, CXR
- Start antibiotic (ceftriaxone, vancomycin)
- Start epinephrine/norepinephrine after 2nd dose

15-40 min

- Establish CVC, ITT
- Start albumin after 60cc/kg
- Titrate epinephrine (0.6BW/100cc DW5%, micro-drop 0.5-15 drop/min) for cold shock
- Titrate norepinephrine (0.6BW/100cc DW5%, micro-drop 0.5-15 drop/min) for warm shock

40-60

- Start hydrocortisone 2-4 mg/kg (up to mg) if catecholamine-resistant shock
- Transfer to PICU