Management of Severe Sepsis & Septic Shock in Infants & Children

Introduction

The inflammatory triad of fever, tachycardia & abnormal perfusion is very common in children with benign infections. Septic shock should be considered in children who manifest this triad but with additional worrying features such as tachypnoea, reduced urine output, irritability, lethargy, drowsiness or an inability to rouse.

The Recognition and clinical diagnosis of septic shock

- Suspected infection
- Hypo or hyperthermia (temp <36°C or >38.5°C)
- Tachycardia
- Tachypnoea
- Altered mental status
- Decreased urine output (<1 ml/kg/min)
- Other end organ dysfunction (see appendix)
- Signs of either cold or warm shock

<table>
<thead>
<tr>
<th>Cold Shock</th>
<th>Warm Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary Refill &gt;3s</td>
<td>Flash Capillary Refill</td>
</tr>
<tr>
<td>Reduced Peripheral Pulses</td>
<td>Bounding Peripheral Pulses</td>
</tr>
<tr>
<td>Cool Mottled Extremities</td>
<td>Warm to edges</td>
</tr>
<tr>
<td>Narrow Pulse Pressure</td>
<td>Wide Pulse Pressure</td>
</tr>
</tbody>
</table>

Hypotension is not required for the *clinical* diagnosis of shock, however once it is present in a child with a suspected infection the diagnosis is confirmed.

Age specific values

<table>
<thead>
<tr>
<th>Age</th>
<th>Tachycardia</th>
<th>Bradycardia</th>
<th>Respiratory Rate</th>
<th>Systolic BP (mmHg)</th>
</tr>
</thead>
<tbody>
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<td>0 - 7 days</td>
<td>&gt;180</td>
<td>&lt;100</td>
<td>&gt;50</td>
<td>&lt;65</td>
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<tr>
<td>1 wk - 1 mo</td>
<td>&gt;180</td>
<td>&lt;100</td>
<td>&gt;40</td>
<td>&lt;75</td>
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<tr>
<td>1 mo - 1 yr</td>
<td>&gt;180</td>
<td>&lt;90</td>
<td>&gt;34</td>
<td>&lt;100</td>
</tr>
<tr>
<td>2 - 5 yrs</td>
<td>&gt;140</td>
<td>N/A</td>
<td>&gt;22</td>
<td>&lt;94</td>
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<tr>
<td>6 - 12 yrs</td>
<td>&gt;130</td>
<td>N/A</td>
<td>&gt;18</td>
<td>&lt;105</td>
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<td>13 - &lt;18 yrs</td>
<td>&gt;110</td>
<td>N/A</td>
<td>&gt;14</td>
<td>&lt;117</td>
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There is now a large body of evidence showing that aggressive optimisation of the haemodynamic status within the first few hours of critical illness has a profound effect in reducing subsequent organ failure and improving overall survival.

Children in septic shock are consistently under-resuscitated in the first few hours.

For every hour that a child remains in Septic Shock the mortality risk doubles.
MANAGEMENT

The First Hour of Resuscitation

GOALS
To restore:
- Normal mental status
- Normal range heart rate for age
- Normal range respiratory rate for age (may not be possible if the underlying cause is pneumonia)
- Capillary Refill Time <3s
- Palpable peripheral pulses
- Normal range blood pressure for age.
- Adequate urine output
- Serum lactate < 2

ACTIONS
1. Maintain or restore a patent airway
2. Give high flow oxygen, intubate if indicated.
3. Obtain secure intravenous access x2 quickly. Do not waste valuable time attempting venous cannulation, if difficult site an intra osseous (IO) needle.
4. Clinical signs of shock should be immediately treated with 20 mls/kg over 5 mins (0.9% saline or colloid).
5. REASSESS
   a. What are the effects on mental status, heart rate, quality of peripheral pulses & CRT?
   b. Is there evidence of volume overload? (hepatomegaly, crackles, increased work of breathing or gallop rhythm)
6. Multiple fluid boluses may be necessary. Large fluid deficits often exist & initial fluid volumes of 40-60 ml/kg are quite usual. Much larger volumes may be necessary.
7. Repeated assessment after each bolus is required. Look for signs of volume overload.
   If volume overloaded do not give further fluids - commence inotropes
8. Give high dose broad spectrum antibiotics
   IV Cefotaxime if under 3 months of age
   IV Ceftriaxone over 3 months and not receiving calcium containing infusions
9. Correct hypoglycaemia & hypocalcaemia
   5 mls/kg 10% dextrose
   0.5 mls/kg 10% calcium gluconate
10. If after 15 minutes of aggressive fluid resuscitation (40-60 mls/kg) there is still evidence of end organ dysfunction start peripheral or IO dopamine
    Up to 10 μg/kg/min
    Keep a close watch on tissue integrity
11. **Use ketamine + suxamethonium to intubate & gain central access.**
12. The 1st choice for central access is FEMORAL. These children are often profoundly coagulopathic. Neck lines therefore carry an increased risk of complication.
13. Insert an arterial line.
14. Reverse **COLD SHOCK**
   a. Titrate central dopamine or if resistant
   b. Titrate central adrenaline
15. Reverse **WARM SHOCK**
   a. Add & titrate central noradrenaline
16. Transfer to PICU

**INDICATIONS FOR INTUBATION**

Impending cardiovascular collapse Poor airway reflexes Depressed level of consciousness – Glasgow Coma Score (GCS) ≤ 8 or AVPU ≤ P Worsening tachypnoea or oxygen requirement. ≥ 60 mls/kg fluid resuscitation *in the first hour* without reversal of shock

**Induction of anaesthesia presents a significant risk** of hypoxia, myocardial depression & afterload reduction.

This can be minimised by
1. Aggressive volume replacement prior to intubation.
2. Having volume running with a bolus attached.
3. Pre Oxygenation with 100% O₂
4. Having a range of endotracheal tubes (ETT). A “good fit” is necessary to ventilate in the face of pulmonary oedema. Use a cuffed ETT if available.
5. Get the most experience person you can find. (eg. Local Anaesthetic or ICU Consultant)
6. Use of Optimal drugs for induction.
   a. Ketamine 0.5-1.0 mg/kg titrated to response
   b. Suxamethonium 1-2 mg/kg (Unless contraindicated)
7. Rapid sequence induction should be considered (NGT + Cricoid pressure).

**Inhalational anaesthetics present a significant risk of cardiovascular depression.**

They should only be used if the risk of a difficult airway out weighs this. Thiopentone, propofol & benzodiazepines all carry a similar risk.
ONCE INTUBATED
1. Confirm endotracheal placement with the use of end tidal CO$_2$ monitoring
2. Ensure ETT is secure
3. Check appropriate position with CXR (Tip at T2-T3)
4. Sedate & Paralyse. Use Morphine & Midazolam as per PICU guidelines with intermittent boluses of non depolarising muscle relaxants
5. These children are at risk of acute respiratory distress syndrome (ARDS). A low tidal volume strategy of 4-7 ml/kg with an initial PEEP of 5 cm/H$_2$O should be used. PEEP can be titrated up depending on blood gases & evidence of pulmonary oedema.

OTHER ISSUES
Coagulopathy
Elevated clotting times should be treated with 10-20 mls/kg of Fresh Frozen Plasma (FFP)
Low platelet counts in the absence of active bleeding should not be supplemented unless $< 20 \times 10^3$/mm$^3$

Do not bolus FFP or platelets, this may cause profound hypotension due to vasoactive kinins & high citrate levels.
Low fibrinogen is suggestive of DIC and should be treated with 5-10mls/kg of Cryoprecipitate.

Electrolytes
Treat Hypomagnesaemia
0.5 ml/kg 20% magnesium sulphate (or 1ml/kg 10% magnesium sulphate)
This can cause hypotension, give slowly over 30 minutes with additional volume if necessary

Treat Hypocalcaemia
0.5 mls/kg 10% calcium gluconate

FOLLOW THE ALGORITHM
There is now a large body of evidence showing that aggressive optimisation of the haemodynamic status within the first few hours of critical illness has a profound effect in reducing subsequent organ failure and improving overall survival.

Children in septic shock are consistently under-resuscitated in the first few hours
(see common mistakes)

Do the simple things well
Management of Severe Sepsis & Septic Shock in Infants & Children

Recognise decreased mental status & perfusion.
Begin high flow O2.
Establish IV/IO access

Initial Resuscitation
Push boluses of 20 mls/kg isotonic saline or colloid up to & over 60 ml/kg until perfusion improves OR hepatomegaly or crackles develop.
Correct hypoglycaemia & hypocalcaemia.
Start Antibiotics.

Fluid Refractory Shock
Start dopamine up to 10 μg/kg/min IV/IO
Intubate & gain central access.

For COLD SHOCK
add in central adrenaline if dopamine resistant.

For WARM SHOCK
add in central noradrenaline.

Catecholamine resistant shock
Begin hydrocortisone IF at risk for absolute adrenal insufficiency.

Cold Shock with normal blood pressure
1. Titrate volume & adrenaline, ScvO2*>70%, Hb >10g/dl
2. If ScvO2 remains <70% add vasodilator with volume loading. (eg. Milrinone)

Cold Shock with low blood pressure
1. Titrate volume & adrenaline, ScvO2*>70%, Hb >10g/dl
2. If remains hypotensive consider noradrenaline.
3. If ScvO2 still <70% add milrinone

Warm shock with low blood inotropes
1. Titrate volume & noradrenaline, ScvO2*>70%
2. If remains hypotensive consider vasopressin, terlipressin or methylene blue.
3. If ScvO2 remains <70% consider low dose adrenaline.

Persistent catecholamine resistant shock
Rule out & correct pericardial effusion, pneumothorax & intra abdominal pressure >12 mmHg.
Consider LiDCO**, Pulmonary artery catheter or doppler ultrasound to guide fluid, inotropes, vasopressor, vasodilator & hormonal therapies.
GOAL Cardiac Index >3.3 & <6.0 l/min/m²

Refractory shock
ECMO

ScvO2* is the saturations taken from a central venous line where the tip is lying at the SVC / RA junction. It is a surrogate for mixed venous saturations.
** LiDCO bolus indicator dilution measurement of cardiac output to calibrate pulse cardiac output monitoring.


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Stabilization : Beyond the First Hour

GOALS
1. Normal perfusion
   a. CRT <3s
   b. No difference in quality between peripheral & central pulses
   c. Warm extremities
2. Urine output >1ml/kg/hr
3. Normal range for age heart rate & respiratory rate (see appendix)
4. Lactate < 2
5. ScvO$_2$ >70%
6. Cardiac Index >3.3 <6.0 l/min/m$^2$

ONGOING FLUID RESUSCITATION
Fluid shift & hypotension secondary to capillary leak can continue for several days. Continued fluid administration should be titrated against clinical end points such as serum lactate, urine output, heart rate, perfusion pressure & cardiac output.
If remains clinically unstable
   Give crystalloid if Hb >10g/dl
   Consider packed red cells if Hb <10g/dl
   Give FFP for deranged clotting profile (infusion never bolus)

Following shock resuscitation; diuretics, peritoneal dialysis or continuous veno veno haemofiltration (CVVH) can be used for those patients who are fluid overloaded & unable to maintain fluid balance with native urine output.

HAEMODYNAMIC SUPPORT
Septic shock is a dynamic process. The agents chosen & initial rates will need to be adjusted according to measured clinical response.

Children with persistent shock have worsening cardiac function & the haemodynamic state may change completely over the first 48 hrs, varying between Low CO/High SVR, Low CO/low SVR & High CO/low SVR.

In critical illness the renal & hepatic functions are altered leading to a change in pharmacokinetics & pharmacodynamics.

The ongoing goal is to maintain a perfusion pressure above the critical point at which blood flow cannot be effectively maintained to meet individual organs requirements.

Ventilation provides cardiovascular support.
Up to 40% of CO may be required to support the work of breathing. This can be reduced by mechanical assistance allowing blood flow to be diverted to other vital organs.
Increased intra thoracic pressure reduces Left ventricular afterload which is particularly helpful in patients with Low CI & high SVR.
Mechanical support also aids patients with increased pulmonary vascular resistance (if ventilated at or around the functional residual capacity (FRC).
Shock with Low Cardiac Index, Normal Blood Pressure & High Systemic Vascular Resistance (Cold Shock with normal BP)

1. Titrate Adrenaline & fluid
   a. Aim ScvO₂ >70%
   b. Hb >10 g/dl
2. If ScvO₂ remains <70% then afterload reduction is the mainstay of treatment to improve ventricular emptying
   Use Milrinone
   Additional volume loading may be necessary.
   Consider alternative vasodilators in recalcitrant low CO

Shock with Low Cardiac Index, Low Blood Pressure & Low Systemic Vascular Resistance (Cold Shock with low BP)

1. Titrate Adrenaline & fluids
   a. Aim ScvO₂ >70%
   b. Hb >10 g/dl
2. If remains hypotensive add Noradrenaline, this increases Diastolic Blood Pressure & SVR.
3. If the ScvO₂ remains <70% once an adequate BP is achieved add Milrinone.

Shock with High Cardiac Index, Low Blood Pressure & Low Systemic Vascular Resistance (Warm Shock with low BP)

1. Titrate Noradrenaline & fluids
   a. Aim ScvO₂ >70%
   b. Hb >10 g/dl
2. If remains hypotensive add low dose vasopressin, terlipressin or methylene blue.
3. These are potent vasoconstrictors & should be used with CO/ ScvO₂ monitoring
4. If ScvO₂ remains <70% add Adrenaline

Refractory Shock

<table>
<thead>
<tr>
<th>Possible cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial effusion</td>
<td>Pericardiocentesis</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Thoracocentesis</td>
</tr>
<tr>
<td>Hypoadrenalism</td>
<td>Adrenal hormone replacement</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Thyroid hormone replacement</td>
</tr>
<tr>
<td>Ongoing blood loss</td>
<td>Transfusion</td>
</tr>
<tr>
<td>Increased intra abdominal pressure</td>
<td>Peritoneal catheter or abdominal release</td>
</tr>
<tr>
<td>Necrotic tissue</td>
<td>Removal</td>
</tr>
<tr>
<td>Uncontrolled source of infection</td>
<td>Use antibiotics with lowest MIC</td>
</tr>
<tr>
<td>Excessive immunosuppression</td>
<td>Reduce immunosuppressants</td>
</tr>
<tr>
<td>Immune compromise</td>
<td>Transfuse for neutropenic patients</td>
</tr>
</tbody>
</table>
Once all the above possible causes have been examined & addressed ECMO becomes a possibility & should be discussed with an ECMO centre. It should however be borne in mind that the overall ECMO survival for sepsis is ≤ 50%.

**Additional Information**

**The Use of Corticosteroids**

If the child is at risk of *absolute* adrenal insufficiency or adrenal pituitary axis failure & remains shocked despite volume resuscitation with the addition of Adrenaline or Noradrenaline infusions then Hydrocortisone may be administered. Ideally a baseline sample should be taken for subsequent determination of the cortisol level.

Hydrocortisone may be given as a bolus or infusion with doses used ranging from 1-2 mg/kg/day (stress cover) to 50 mg/kg/day (titrated to reversal of shock).

**At risk patients**

- Purpura fulminans
- Congenital adrenal dysplasia
- Recent steroid exposure
- Known hypothalamic/pituitary dysfunction

The concept of “relative” adrenal insufficiency as a consequence of severe sepsis has been discussed for some years. Some research (mostly adult) has indicated an improvement in outcome, whilst others studies have shown a worsening in outcome.

There is currently insufficient paediatric data & whilst trials are ongoing Corticosteroids should be considered with caution. Discuss with PICU prior to use.

**The use of Thyroid Hormones**

Replacement of thyroid hormones can be lifesaving in patients with thyroid insufficiency.

Hypothyroidism is relatively common in children with Trisomy 21 & those with central nervous pathologies.

**Fluid Restriction in meningitis**

The latest guidance from NICE suggests non-fluid restriction in meningitis. The forum has discussed this with the PICU leads who currently would like to continue with the common management of fluid restriction in meningitis but ensuring that shock is corrected and in a normal perfusion state. Discuss with PICU for advice if any doubt.
Common Errors

Failure to establish vascular access in the severely shocked child
Do not persist in peripheral access
Use an intraosseous needle for rapid easy central access

Inadequate fluid resuscitation
Give 20 mls/kg and reassess
These patients often require 100-200 mls/kg
Large volume requirements = severe disease, titrate fluids to CVP and ScvO₂ >70%

Failure to recognise volume overload
Increasing work of breathing with worsening oxygenation following fluid administration is suggestive of volume overload. Crackles on auscultation do not absolutely indicate pulmonary oedema as a pneumonic process may be the underlying source of sepsis.
Hepatomegaly is highly suggestive of volume overload.
If unsure apply gently pressure over the liver (transiently increasing right atrial filling) & watch the HR, BP & CVP response.

Delay in intubation
Children in comparison to adults delay a drop in blood pressure by vasoconstriction & elevation of heart rate. A “normal” blood pressure can be falsely reassuring.
Once hypotension occurs there is usually a rapid progression to cardiovascular collapse.
A planned intubation is required (see intubation indications)

False reassurance after initial response to resuscitation
Reassess, reassess, reassess

Indicators of disease severity regardless of “how good they look”
Low neutrophils
Low platelets
Rapid onset (<6 hours)
Rapidly spreading rash
High volume requirement
References
Appendix

Definitions

Systemic Inflammatory Response Syndrome (SIRS)
The presence of at least two of the following four criteria, one of which must be abnormal temperature or leucocyte count.

• Core temperature of >38.5°C or <36°C

• Tachycardia, defined as a mean heart rate >2 SD above the normal for age in the absence of external stimulus, chronic drugs or painful stimuli or otherwise persistent elevation over 0.5 - 4 hr time period, or for children < 1yr bradycardia; or otherwise persistent depression over 0.5 hr time period.

• Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an 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 leucocytes.

Infection
A suspected or proven (by culture, tissue stain or polymerase chain reaction test) infection 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 tests (eg white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash or purpura fulminans)

Sepsis
SIRS in the presence of or as a result of suspected or proven infection.

Severe sepsis
Sepsis plus one of the following; cardiovascular organ dysfunction or acute respiratory distress syndrome or two or more other organ dysfunctions.

Septic shock
Sepsis and cardiovascular organ dysfunction.
Age specific values

<table>
<thead>
<tr>
<th>Age</th>
<th>Tachycardia</th>
<th>Bradycardia</th>
<th>Respiratory Rate (bbm)</th>
<th>Leucocyte count x10^3 mm</th>
<th>Systolic BP (mmHg)</th>
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<td>&lt;100</td>
<td>&gt;40</td>
<td>19.5 or &lt;5</td>
<td>&lt;75</td>
</tr>
<tr>
<td>1 mo - 1 yr</td>
<td>&gt;180</td>
<td>&lt;90</td>
<td>&gt;34</td>
<td>17.5 or &lt;5</td>
<td>&lt;100</td>
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<tr>
<td>2 - 5 yrs</td>
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<td>15.5 or &lt;6</td>
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<td>6 - 12 yrs</td>
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<td>13.5 or &lt;4.5</td>
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<tr>
<td>13 - &lt;18 yrs</td>
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<td>N/A</td>
<td>&gt;14</td>
<td>11 or &lt;4.5</td>
<td>&lt;117</td>
</tr>
</tbody>
</table>

Organ Dysfunction criteria

Cardiovascular

• Despite administration of isotonic fluid boluses ≥ 40 mls/kg in 1hr
• Hypotension (BP <5th centile for age) or Systolic BP < 2 SD below normal for age
  OR
• Need for vasoactive drugs to maintain BP in normal range (Dopamine >5 mcg/kg/min or Dobutamine, Adrenaline or Noradrenaline at any dose)
  OR
• Two of the follow
  • Unexplained metabolic acidosis: base deficit >5 mEq/L
  • Increased arterial lactate > 2x upper limit of normal
  • Oliguria: urine output < 0.5 ml/kg/hr
  • Prolonged capillary refill >5s
  • Core to peripheral temperature gap >3°C

Respiratory

• PaO2/FiO2 <300 in the absence of cyanotic heart disease or preexisting lung disease
• PaCO2 > 65 torr or 20 mmHg over baseline PaCO2
• Proven need for >50% O2 to maintain saturation ≥ 92%
• Need for non elective invasive ventilation or non invasive mechanical ventilation

Neurology

• Glasgow Coma Score ≤ 11
• Acute change in mental status with decreased GCS ≥ 3 points from abnormal baseline

Haematology

• Platelet count < 80 x10^3/mm^3
  OR
• A decline of 50% in platelet count from highest value recorded over past 3 days (for chronic haematology/oncology patients)
• International Normalised Ratio >2
Renal

• Serum creatinine $\geq$ 2x upper limit of normal for age
  OR
• A x2 increase in baseline creatinine

Hepatic

• Total bilirubin $\geq$ 4 mg/dl OR
• ALT x2 upper limit of normal age
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Retrieval Process

These patients often deteriorate rapidly following their presentation.

**At Referral Call**
Establish who you are talking to & introduce yourself.  
Who else is present (Senior Paediatrician, Anesthetist, ICU)?  
Conference in the PICU Consultant.  
Obtain a brief history of presentation.  
What was the clinical status on arrival & how long ago was this?  
Ascertain the current status & what interventions have been performed since arrival.

**Airway & Breathing**
What are the saturations?  
What were they in air?  
Has the patient been intubated?  
What are the current ventilator settings or are they being hand bagged?  
If not intubated are there markers of Respiratory distress?  
What is the respiratory rate? Is there recession / grunting? If preparing for intubation Who is going to do it?  
What agents are they planning to use?  
What does the CXR show?

**Circulation**
What were the Heart Rate, Capillary refill, Blood pressure on presentation?  
What are they now?  
What fluids have been given & over what time period?  
What vascular access has been obtained?  
If access is a struggle suggest **IO or external jugular route**  
Have inotropes been started?  
If so which ones & at what dose?  
Is there Central & Arterial access?  
If so, what are the central venous saturations (ScvO2)?  
If not, request this be obtained with the support of the local anaesthetic/ ICU team

*Note*
ScvO2 is the saturations taken from a central venous line where the tip is lying at the superior vena cava (SVC) / right atrium (RA) junction. It is a surrogate for mixed venous saturations.

**Disability**
What was the Level of Consciousness on arrival? AVPU  
If given GCS ask for the “split” (motor, verbal, eye). People often estimate a number What is it now?  
Is there evidence of raised intra cranial pressure?  
Cushings Triad (elevate systolic & decreased diastolic BPs + bradycardia)  
Is there evidence of meningism?  
What is the urine output?  
If not catheterised request this to be done when practicable
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**Drugs**
What antibiotics have been given?
Consider broadening cover
Aciclovir for disseminated herpes simplex virus (HSV), neonates are most at risk
*Only give steroids if there is an absolute risk of adrenal hypo responsiveness*  
eg. Long term steroids use  
- Known pituitary or adrenal disease  
or treatment is being for suspected meningitis

Was a random cortisol taken before this?
* discuss with PICU Consultant first.

**Exposure**
Is there a rash? - blanching vs. non blanching

**Electrolytes etc**
BM  
FBC remember platelets x neutrophils (PN) <40 is highest risk
Clotting profile only supplement low platelets if active bleeding or < 20
U&Es correct Ca^{2+} & Mg^{2+} derangement
LFTs hepatitis associated with disseminated HSV