Neonatal sepsis

Definition

- Neonatal septicemia is defined as generalized systemic features of infection,associated with pure growth of bacteria from one or more sites,in a newborn.
- It is one of the most important causes of mortality and morbidity in newborn

(especially in preterm,LBW babies).

- According to NNPD,

-incidence of neonatal sepsis is about 30 per 1000 live births

-incidence of mortality due to NNS is about 4.1 %

- If diagnosed early and treated aggressively with antibiotics & good supportive care,most cases of neonatal sepsis can be saved.

- When pathogenic bacteria gain access into the blood stream,
  - they may cause overwhelming infection without much localization (septicemia),
  - may get predominantly localized to the lung (pneumonia),
  - the meninges (meningitis).

Classification

- Neonatal sepsis can be classified into two sub-types depending upon time of onset of symptoms

Before 72 hours of life (early onset sepsis)

After 72 hours of life (late onset sepsis)

Early onset sepsis

- Mainly due to bacteria acquired before and during delivery

i.e, by organisms prevalent in genital tract or in the labor room or O.T

- Mostly caused by Gram –ve organisms(e coli,klebsiella,enterobacter,group B streptococci)
- Majority manifest as RD due to intrauterine pneumonia

The associated factors for early-onset sepsis include :

- Prolonged rupture of membranes > 12 hours
- Foul smelling liquor or MSL
- Multiple per vaginal examination
- Maternal fever during or within 2 weeks of delivery
- Very low birth weight or preterm baby
- Difficult or prolonged labor
- Birth asphyxia and difficult resuscitation
- Pathological evidence of funisitis or presence of polymorphs in gastric aspirate

- Prolonged rupture of membranes(PROM) : the risk of sepsis is 1% percent compared to a baseline incidence of 0.3% .
- Chorioamnionitis : increases the risk by 2 to 3 times.
- Prematurity & low birth weight : 10 times higher risk of than term and normal birth weight infants.

- Perinatal asphyxia : asphyxia is associated with depressed immune function & interventional procedures increase the risk of infection by 4%
- Male gender : boys have 2 to 6 times higher risk

Late onset sepsis

- Caused by the organisms of the external environment of home or hospital.
- Often transmitted through the hands of the care-providers.
- 2/3rds by Gram –ve organisms (ecoli,klebsiella,enterobacter,serratia,pseudomona, proteus,citrobacter)

- 1/3rds by Gram +ve organisms (Coagulase positive staph aureus,CONS)

- Presentation is that of septicemia, pneumonia or meningitis.

- Sequelae in survivors of meningitis are usually severe.

- The associated factors of late-onset sepsis include:

  - Low birth weight
  - Preterm babies (PDA,NEC,BPD)
  - Delayed enteral feeding
  - Superficial infections (pyoderma, umbilical sepsis)
  - Mechanical ventilation
  - Presence of central venous catheters,percutaneous catheters

- Case definitions of NNS acc. to NNF :
  - Proven sepsis : clinical picture of sepsis & isolation of pathogens from blood,csf,urine or other body fluids
  - Probable sepsis : clinical picture suggestive of sepsis

    with lab investigations s/o sepsis

    but blood culture sterile .

- Sepsis syndrome : septicemia associated with altered organ perfusion(hypoxia,lactic acidosis,oliguria & altered mental status)

- If untreated,leads to early septic shock,can be reversible with appropriate treatment.
- If untreated,this state progresses to refractory shock & multi organ dysfunction.

Clinical features

- The early diagnosis of NNS is difficult since most of the symptoms & signs are non specific.
- The possibility of sepsis must be considered with any clinical deterioration unless the event is readily explained by other causes.
- For every 15 non infected newborns treated in NICU only one newborn has documented infection.

Lethargy	Cyanosis*
Refusal to suckle	Tachypnea*
Poor cry	Chest retractions*
Not arousable, comatosed	Grunt*
Abdominal distension	Apnea/gasping*
Diarrhea	Fever+
Vomiting	Seizures+
Hypothermia	Blank look+
Poor perfusion	High pitched cry+
Sclerema	Excessive crying/irritability+
Poor weight gain	Neck retraction+
Shock	Bulging fontanel+
Bleeding	
Renal failure	

* Particularly suggestive of pneumonia

+ Particularly suggestive of meningitis

- The most common manifestation is :

- respiratory distress in EOS

- alteration in the established feeding behaviour in LOS.

- Hypothermia is a more common manifestation of sepsis than fever.
- Pyelonephritis is common in males and preterms,enlarged palpable kidneys +

- Sclerema – hide like character of skin,
  skin stretched over underlying structures,
  becomes unpinchable,
  starts over face and legs and advances centripetally,
  if skin over chest involved -> breathing becomes shallow and rapid.

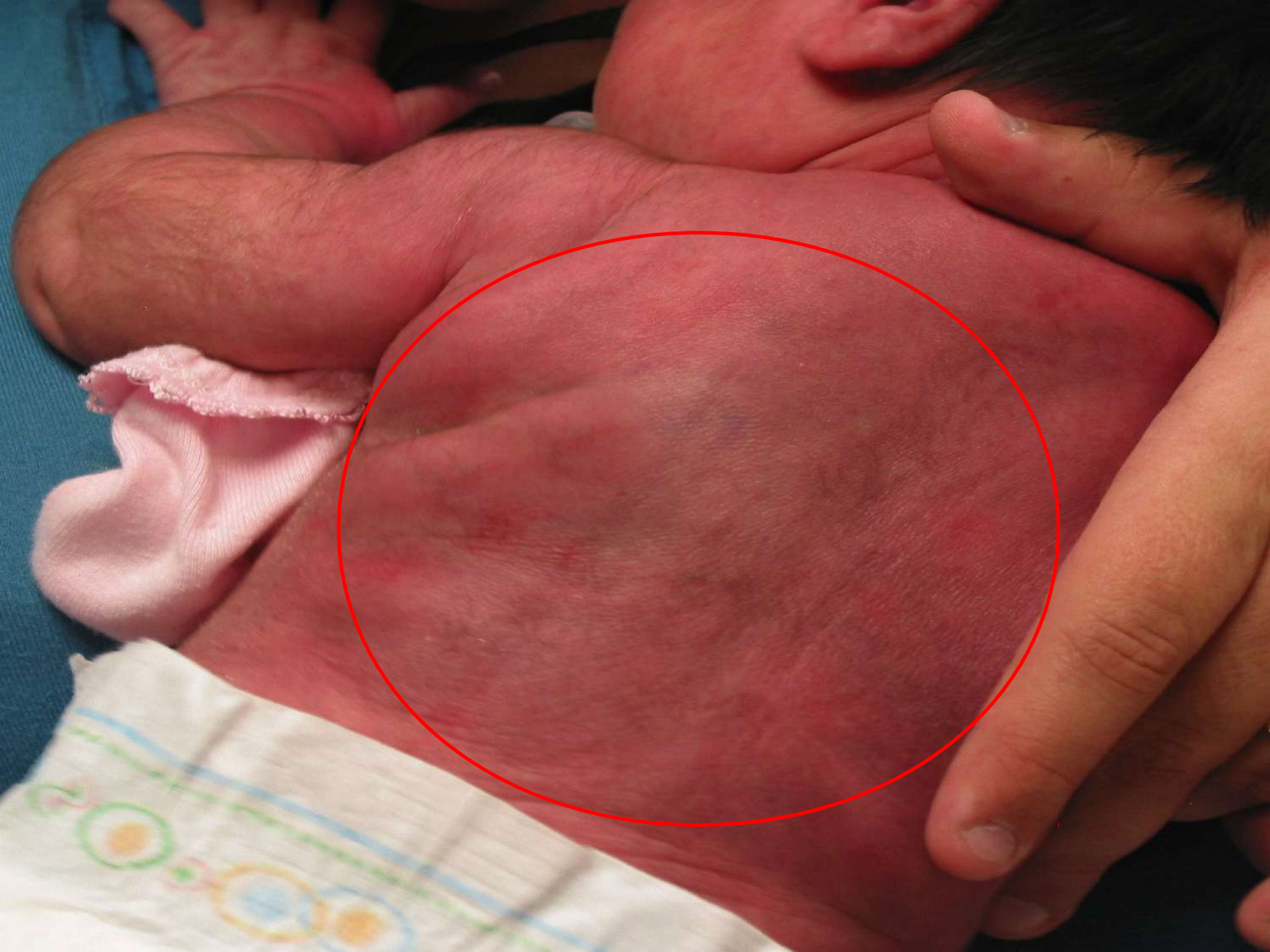
- NEC presents as distended abdomen,
  passage of blood/mucus per rectum,
  bilious vomiting,
  diminished or absent bowel sounds,
  peritonitis,
  stool is positive for occult blood

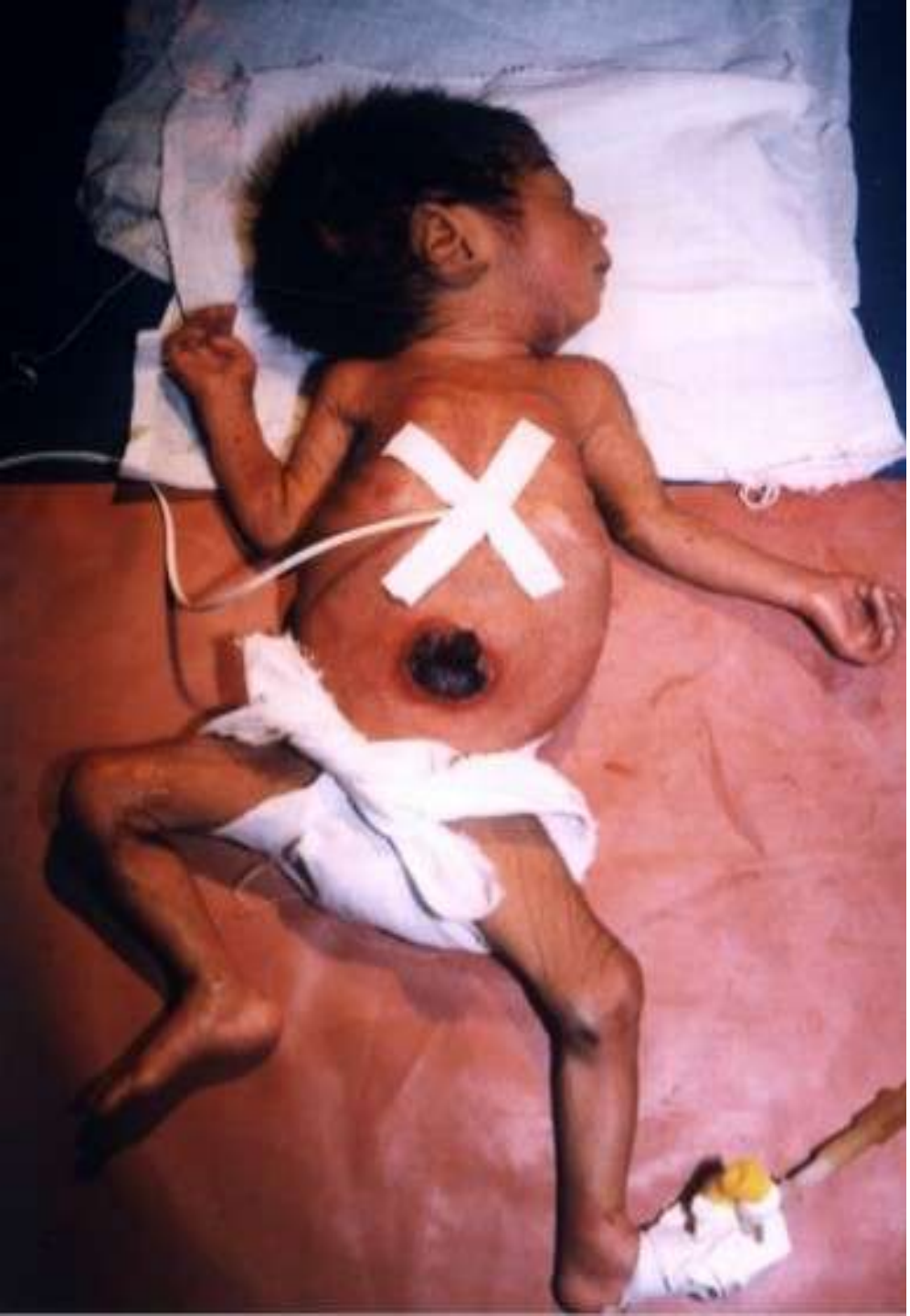
- Any bone may be involved in osteomyelitis.
- Septic arthritis is more common in hip,knee,wrist joints - swollen,red,tender,movement is limited.
- If child goes into shock -> cool peripheries,prolonged CFT,peripheral pulses absent,pale ashen gray look.
- If prolonged acidosis/hypothermia -> DIC with bleeding manifestations.

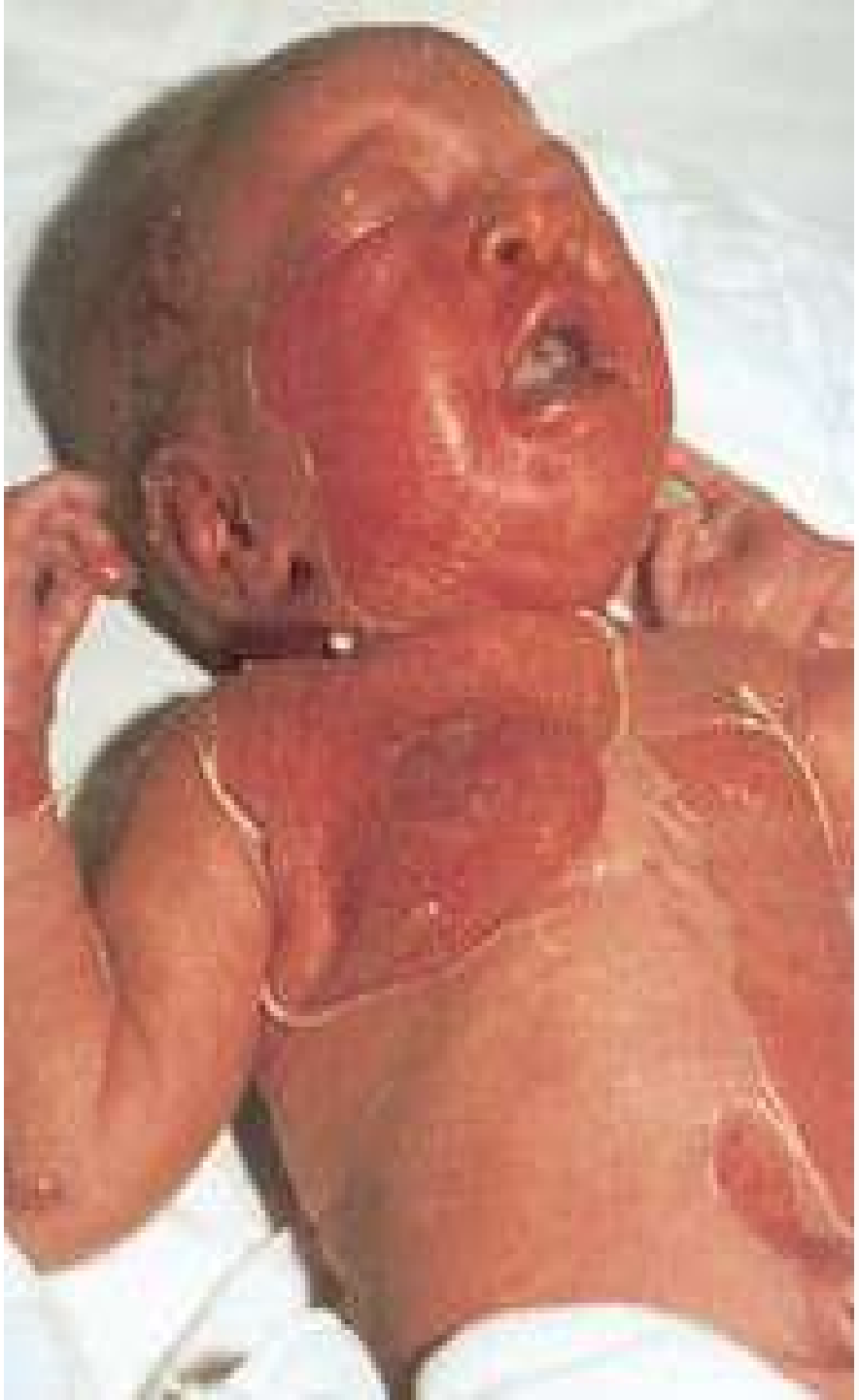
Clinical suspicion of etiologic agent

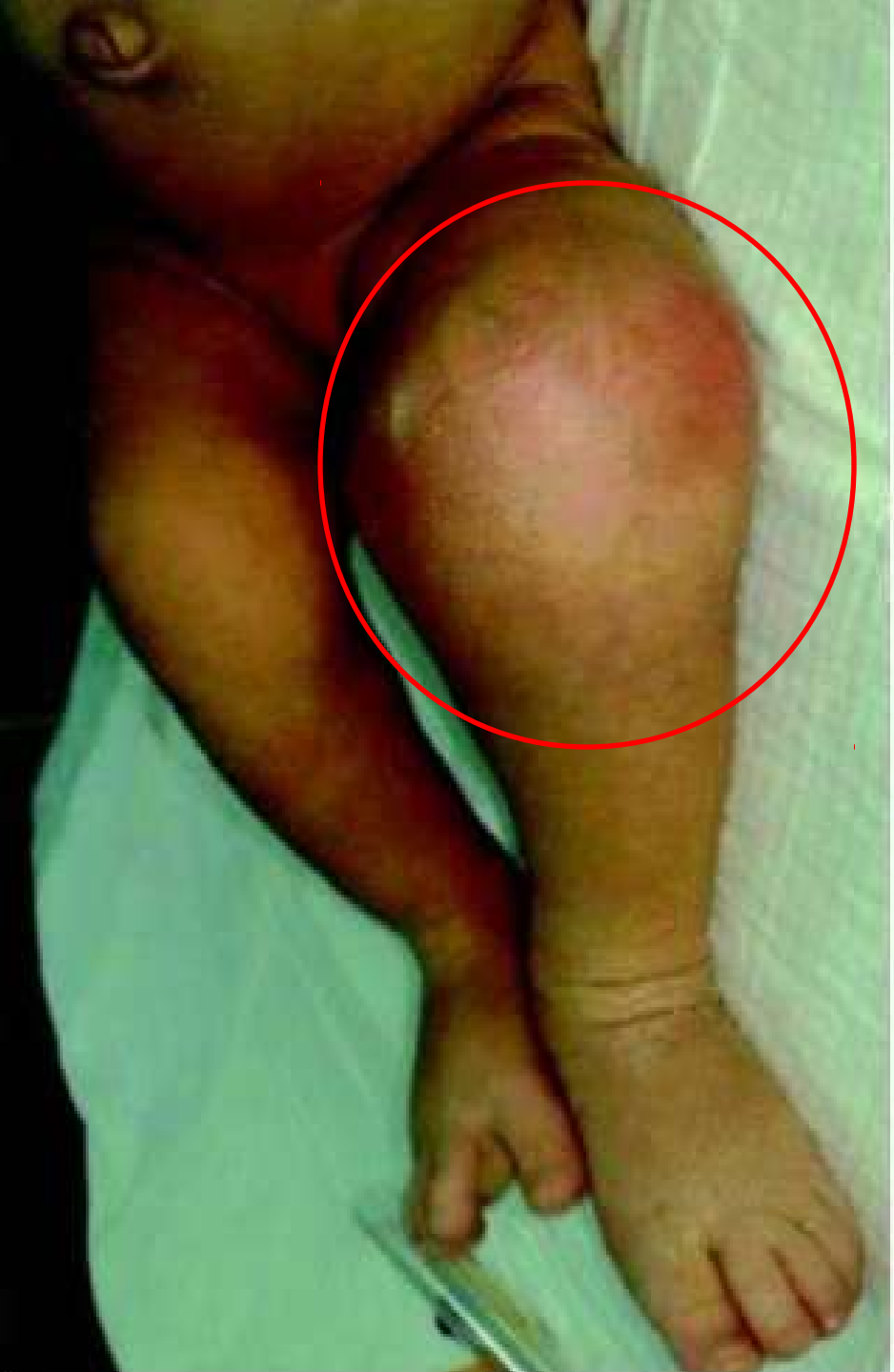
- Staphylococcus – usually after 72 HOL,present as pyoderma,conjunctivitis,umbilical sepsis,abscess,osteomyelitis,scalded skin syndrome.
- Listeria – peripartal maternal fever,G.E + MSL,baby limp at birth,AF depressed,RDS,apnoea,skin rash,hepatosplenomegaly.
- Pseudomonas
- Klebsiella

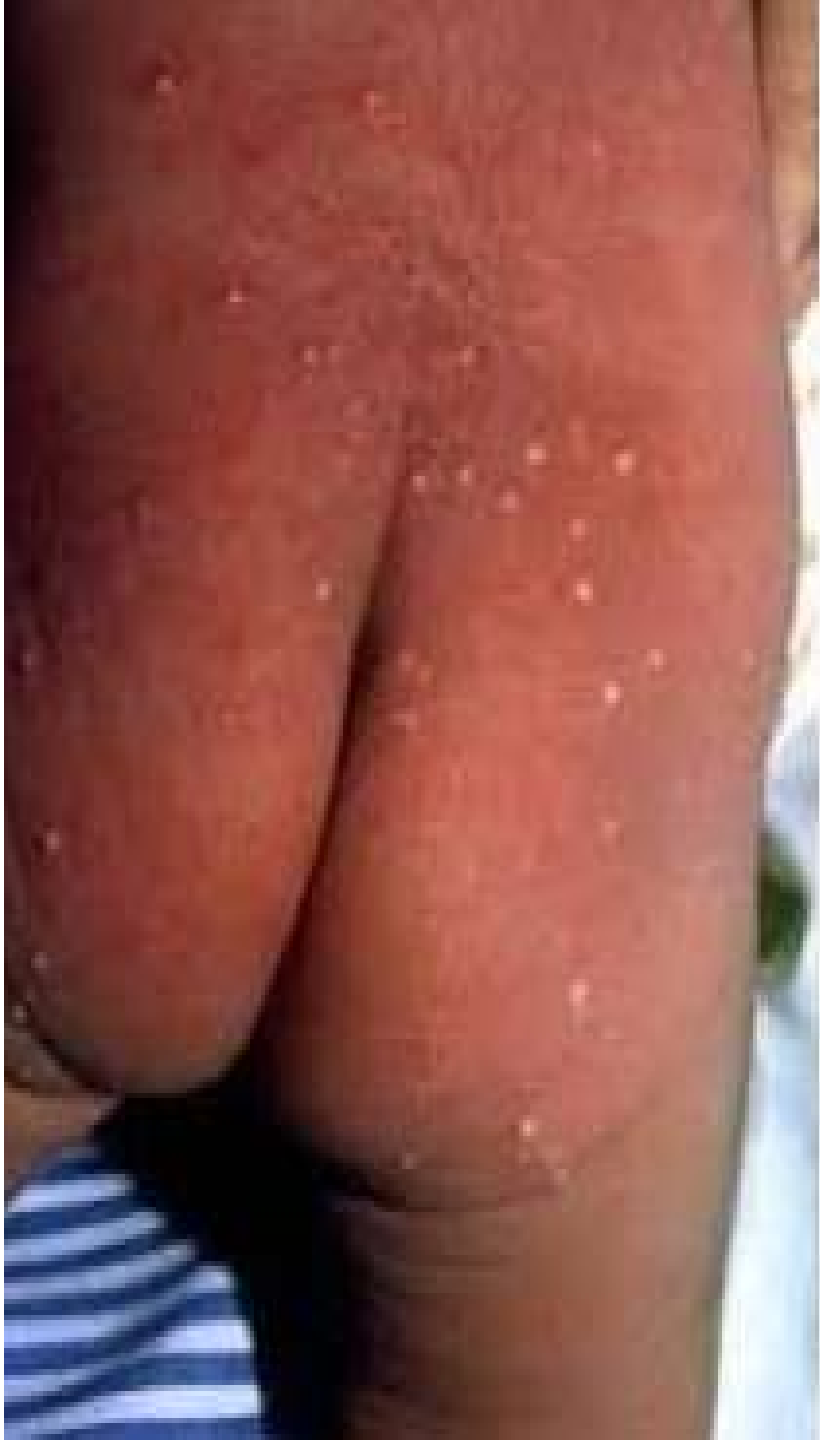
} grayish black gangrenous patches on the skin











Diagnostic tests

Definitive,Specific

- Blood culture
- CSF culture
- Urine culture
- Tracheal aspirate culture
- Polymerase chain reaction
- Latex particle agglutination test

Nonspecific,Diagnostic

- White blood cell count
- C-reactive protein(CRP)
- Micro ESR
- Other acute phase reactants

Definitive,specific tests

Blood culture

- Venipuncture site thoroughly sterilized
- Alcohol-povidone iodine-alcohol
- Dry for 30 seconds
- Take 1ml of blood in a 10-20ml broth (blood sample is 5-10% of broth volume)
- The blood culture should be incubated for at least 72 hours before being considered negative
- The late growing organisms are anaerobes & CONS
- BACTEC,BACT/ALERT method is superior(fast result,greater yield)
- Though blood culture is gold standard,it is positive in only 60% cases

CSF examination

- Always do LP in a suspected case of LOS.

COMPONENTS	NORMAL FINDINGS
★ Total cells (mm^3)	8 (0-30)
★ Polymorphonuclear cells (%)	60%
★ Protein (mg/dl)	90 (20-170)
★ Glucose (mg/dl)	52 (34-119)
★ CSF to blood glucose ratio (%)	51 (44-248)

- > 30 WBC/mm3 ,with > 60% PMN,glucose < 50% of blood glucose,protein > 150 mg/dl in term and >180mg/dl in preterms suggest meningitis.

Urine examination

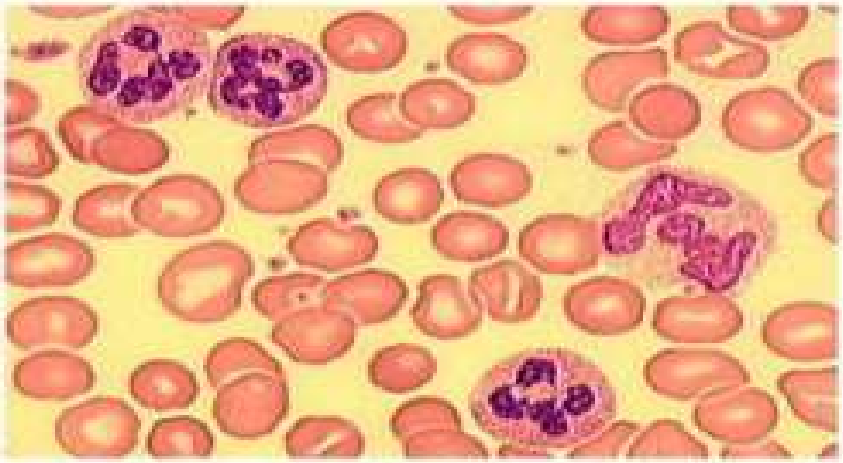
- Suprapubic specimen of urine is ideal.
- >10 WBC/mm3,colony count of >10 power 4 organisms/ml of urine suggest pyelonephritis.

Nonspecific,diagnostic,septic screening tests

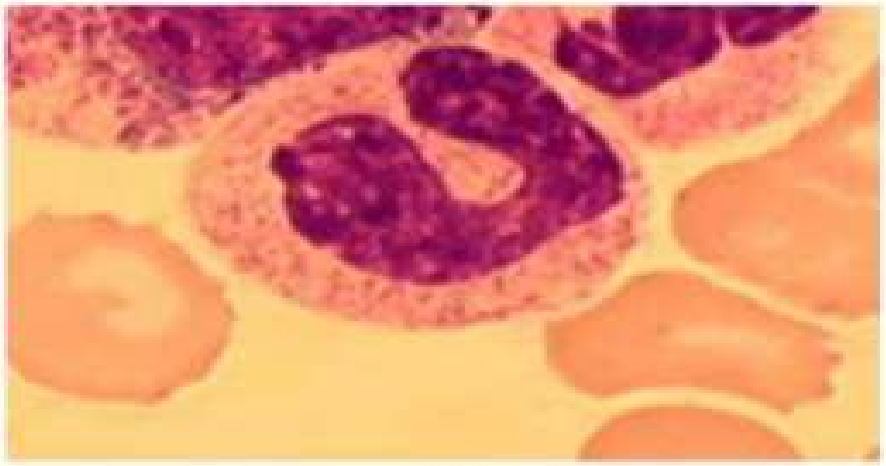
- Indicate infection without identifying the organisms

LEUKOCYTES

1. TLC of 8000-20000 is normal in neonates -> non specific
2. Leukopenia(<5000) or absolute neutropenia (<1000) suggest sepsis
3. Band cell count of >20% and band count : total neutrophil count >0.2
4. Abnormal neutrophils(Dohle bodies,toxic granulations,vacuolization)



Mature neutrophil



Band cell

Micro ESR

- Inexpensive & easy bedside screening test for neonatal sepsis.
- Normal values increase with postnatal age

= day of life plus 3mm

(upto a maximum of 15 mm).

- >15mm suggests infection.
- Less sensitive.

C-reactive protein

- CRP is synthesized by the liver following any inflammation.
- Most reliable indicator of neonatal infection.
- A level of >1mg/dl is considered abnormal in a neonate.
- A single value of negative CRP -> not of much significance.
- In suspected cases,repeat CRP after 12 hours.
- Serial decline in CRP levels with therapy indicates infection responding well to antibiotics.
- Elevation of CRP precedes relapse of infection.

Other acute phase reactants

- Prealbumin ,fibronectin and transferrin are negative reactants.
- Procalcitonin is produced in plasma of infected patients,

  physiologically elevated during 1st three days of life,

  normal value of 0.5,

  indicator of late onset sepsis,

  more reliable than CRP.

Those increasing with inflammation

- C-reactive protein
- Procalcitonin
- Cytokines (IL-6 and IL-1ra)
- Alpha 1-acid glycoprotein (orosomucoid)
- Haptoglobin (alpha-2 glycoprotein)
- Alpha 1-antitrypsin

Those decreasing with inflammation

- Elastase-alpha-1-proteinase inhibitor
- Fibrinogen
- Prealbumin
- Transferrin

Miscellaneous tests

- Endotoxin release assay.
- NBT reduction by neutrophils.
- Gastric aspirate -> More than 5 neutrophils/HPF indicate exposure to chorioamnionitis.
- Pus smear

Sepsis screen

- Done to rule out sepsis rather than to rule in sepsis.
- Consists of :
  - C-reactive protein (CRP),
  - Total leukocyte count(TLC),
  - Absolute neutrophil count (ANC),
  - Immature to total neutrophil ratio (ITR),
  - micro-erythrocyte sedimentation rate (µ-ESR)

Parameter	Abnormal value
✶ Total leukocyte count	< 5000/mm^3
✶ Absolute neutrophil count	Low count as per Manroe chart for term infants and Mouzinho chart for VLBW babies
✶ Immature (band cells) to total neutrophil ratio	>0.2
✶ Micro-ESR	>15 mm 1st hour
✶ C-reactive protein (CRP)	> 1 mg/dl

- Two or more parameters of the sepsis screen are positive -> sepsis screen positive
- If all the parameters of the sepsis screen are negative in a neonate -> low probability of sepsis , antibiotics need not be started and the neonate must be monitored clinically.
- The screen must be repeated after 12 hours.
- Two consecutive completely negative screens are suggestive of no sepsis.

Evaluation of extent of the disease

- LP for meningitis
- Urine examination
- CXR
- Xray erect abdomen
- Stool for occult blood
- Bone scan

Look for biochemical abnormalities

- Blood glucose
- Blood urea
- Serum creatinine
- TSB
- Serum electrolytes
- ABG

Management

Early recognition

+

Appropriate antibiotic therapy

+

Optimal supportive measures

Specific antimicrobial therapy

- High index of suspicion + positive sepsis screen

Start antibiotics

(depending upon the prevalent bacterial flora and sensitivity pattern specific to each NICU).

- Constant reviewing and modifying the choice of antibiotics to be done as flora and susceptibility patterns keep changing.
- Periodic changes prevent emergence of antibiotic resistance.

- Combination antibiotics covering most of the pathogens to be started initially.
- Aminoglycoside + ampicillin.
- Cephalosporins,vancomycin,impinem reserved for life threatening infections and meningitis.
- In centers with high incidence of resistance to cephalosporins,start piperacillin-tazobactum/methicillin-vancomycin.

- Newer antibiotics -> aztreonam,meropenem.
- Infections due to ESBL organisms should be treated with meropenem.
- If meningitis -> cefotaxime/ceftazidime + amikacin.

If etiological agent identified or highly suspected based on clinical picture -> start highly specific antibiotic

- GBS – ampicillin or benzyl penicillin
- E .coli,Klebsiella – cefotaxime or ampicillin + gentamicin
- Listeria – ampicillin + gentamicin
- Enterobacter,serratia - piptaz or vancomycin + gentamicin
- Enterococcus – ampicillin or vancomycin + gentamicin
- Pseudomonas – ceftazidime or cefepime
- MRSA – Vancomycin
- CONS –Vancomycin

Duration of antimicrobial therapy

✶ Culture and sepsis screen negative but clinical picture suggestive of sepsis	5-7 days
✶ Sepsis screen positive but blood/CSF culture negative	7-10 days
✶ Blood culture positive but no meningitis	10-14 days
✶ Meningitis (irrespective of culture report)	21 days
✶ Arthritis, osteomyelitis, endocarditis	4-6 weeks
✶ Ventriculitis	6 weeks

Supportive measures

- Nursed in ambient temperature
- IVF started and enteral feeding stopped for few days
- Correct hypoglycemia by 10% D bolus
- Inj Vit-K given iv twice a week till enteral feeds re-established
- Sodabicarb to correct metabolic acidosis
- Treat shock with volume expanders,dopamine
- FFP to correct poor perfusion
- Corticosteroids given in very sick neonates with endotoxic shock,sclerema,adrenal insufficiency

- Phototherapy and exchange transfusion for hyperbilirubinemia
- Oxygen and ventilatory support if respiratory failure
- Gentle physical stimulation if apneic
- Drainage of abscesses
- Bleeding tendencies managed by vit K,FFP,fresh blood,platelet transfusions
- Treat seizures

Newer therapies

- **a) Intravenous immunoglobulins (IVIG):** Under study.Not much data to support use of IVIG. IVIG 500-1000 mg/kg/dose. Specific Immunoglobulins : Anti GBS Ig.

- **b) Colony stimulating factors:** No evidence to support the use of CSF either as a treatment modality or as a prophylaxis therapy.

G – CSF 10 μg/kg/d for 3 days

GM – CSF 10 μg/kg/d for 5 days

- **c) Blood Exchange Transfusion (BET):** BET may be performed in a case of deteriorating sepsis with sclerema provided the general condition of the baby allows the procedure.
- **d) Oral administration of IgA and IgG in NEC**
- **e) Granulocyte infusions**

Prevention

* Handwashing
* Isolation?
* Bedside asepsis
* Disposal of waste products in separate bins
* Glucose, protein, and lipid solutions should not be reused
* Intravenous in-line bacterial and viral filters
* Avoid overcrowding
* Adequate staff
* Periodic surveillance
* Regular cleaning of the unit
* Exclusive use of breast milk
* Treat LOS as a medical emergency

Thank You !!