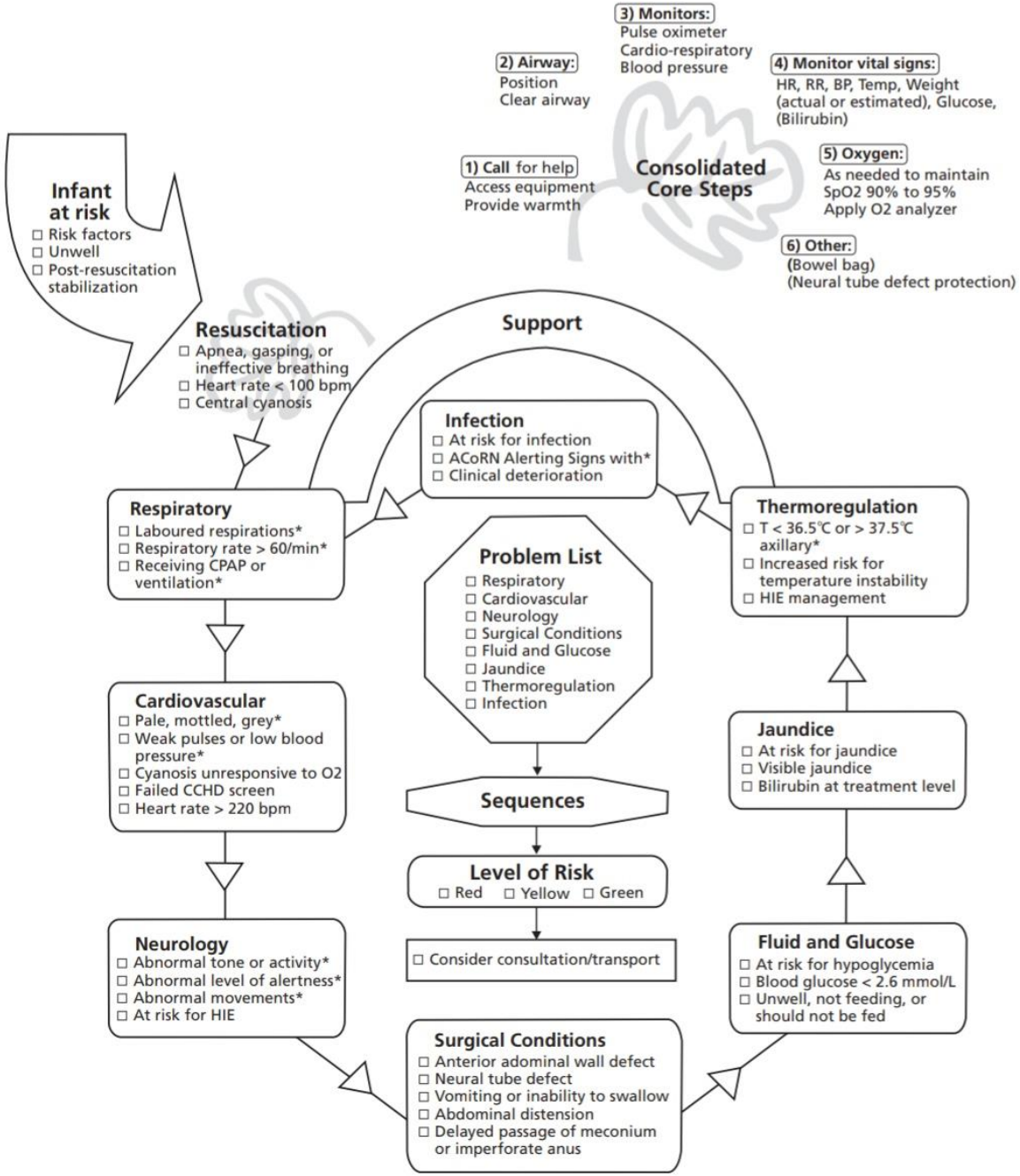
# ACoRN Infection Sequence

Dr.Dehvari
neonatologist

## The ACoRN Primary Survey



- 1 in 1000 liveborn infants present with infection in the perinatal period
- Incidence is higher in preterm infants
- EOS is defined as invasive infection in the first 72 h of life
- Intrapartum maternal antibiotics have been shown to decrease the incidence of EOS from GBS

# Intrapartum antibiotic prophylaxis

- Have a positive GBS screen or have had GBS bacteriuria at any time during pregnancy,
- • Have had a previous infant with invasive GBS infection,
- • Have unknown GBS status and have risk factors such as preterm labour or premature rupture of
- membranes (PROM) greater than or equal to 18 h,
- • Develop a fever of greater than 38oC during labour, *or*
- • Have suspected or definitive chorioamnionitis

- Appropriate IAP reduces risk for early- onset GBS sepsis significantly but does not reduce the incidence of late- onset GBS disease
- GBS disease occurs in the presence of negative maternal GBS cultures and, occasionally, following adequate IAP
- IAP does not affect the frequency of sepsis caused by organisms other than GBS.

# LOS

- infection occurring after the first 72 h post-birth
- typically nosocomial (hospital- acquired) or community- acquired
- prematurity and admission to hospital
- indwelling lines or tubes
- LOS may affect up to 20% in preterm infants admitted to a NICU

# ‘sepsis’

- 95% of newly born infants who have sepsis show clinical signs within 24 h of infection onset
- sepsis is most commonly bacterial

# Noninfectious conditions can present with sepsis- like signs

- • Ductus- dependent congenital heart disease,
- • Congenital adrenal hyperplasia,
- • Inborn errors of metabolism, and
- • Abdominal catastrophe (e.g., bowel malrotation with volvulus).

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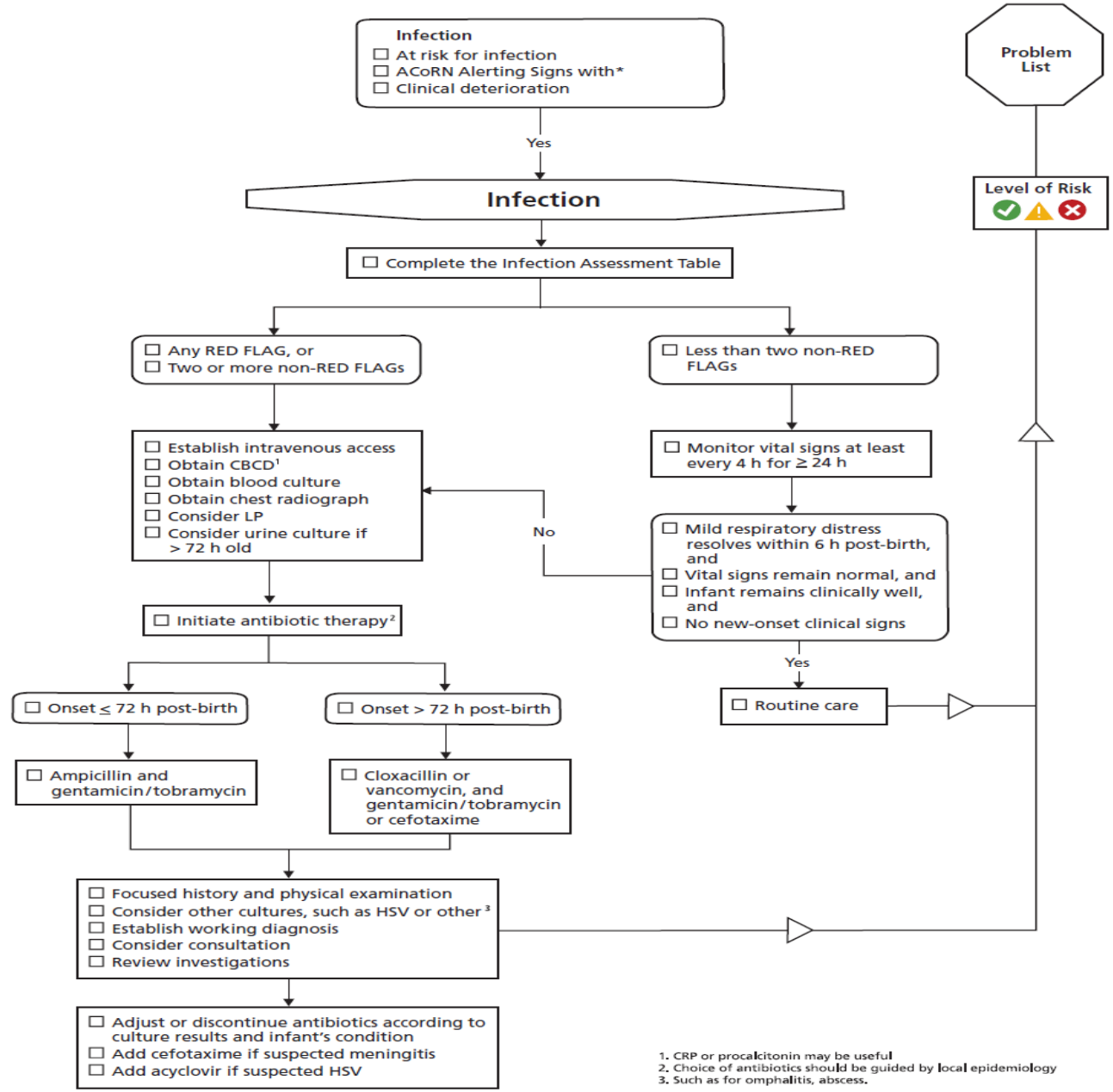


1. CRP or procalcitonin may be useful
2. Choice of antibiotics should be guided by local epidemiology
3. Such as for omphalitis, abscess.

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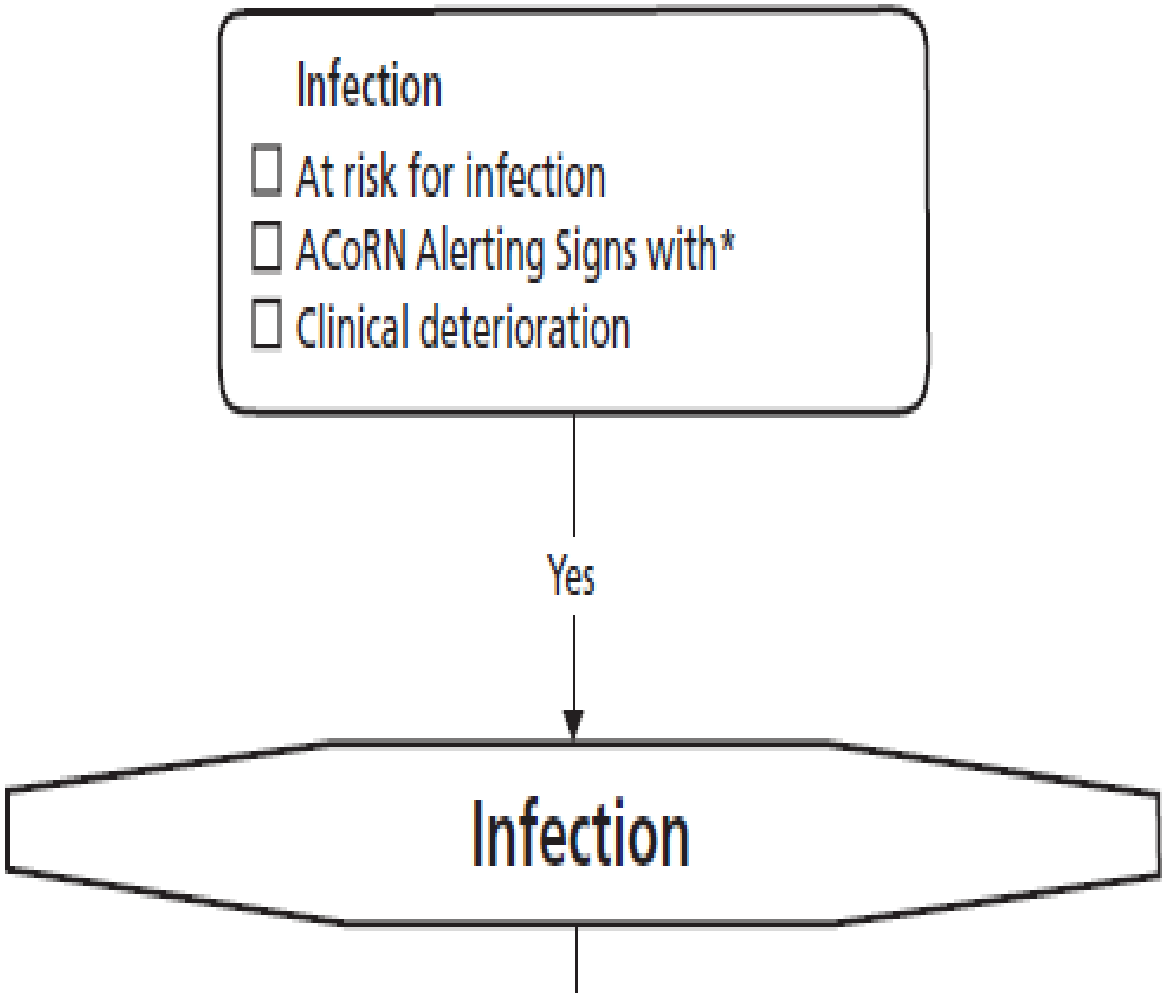
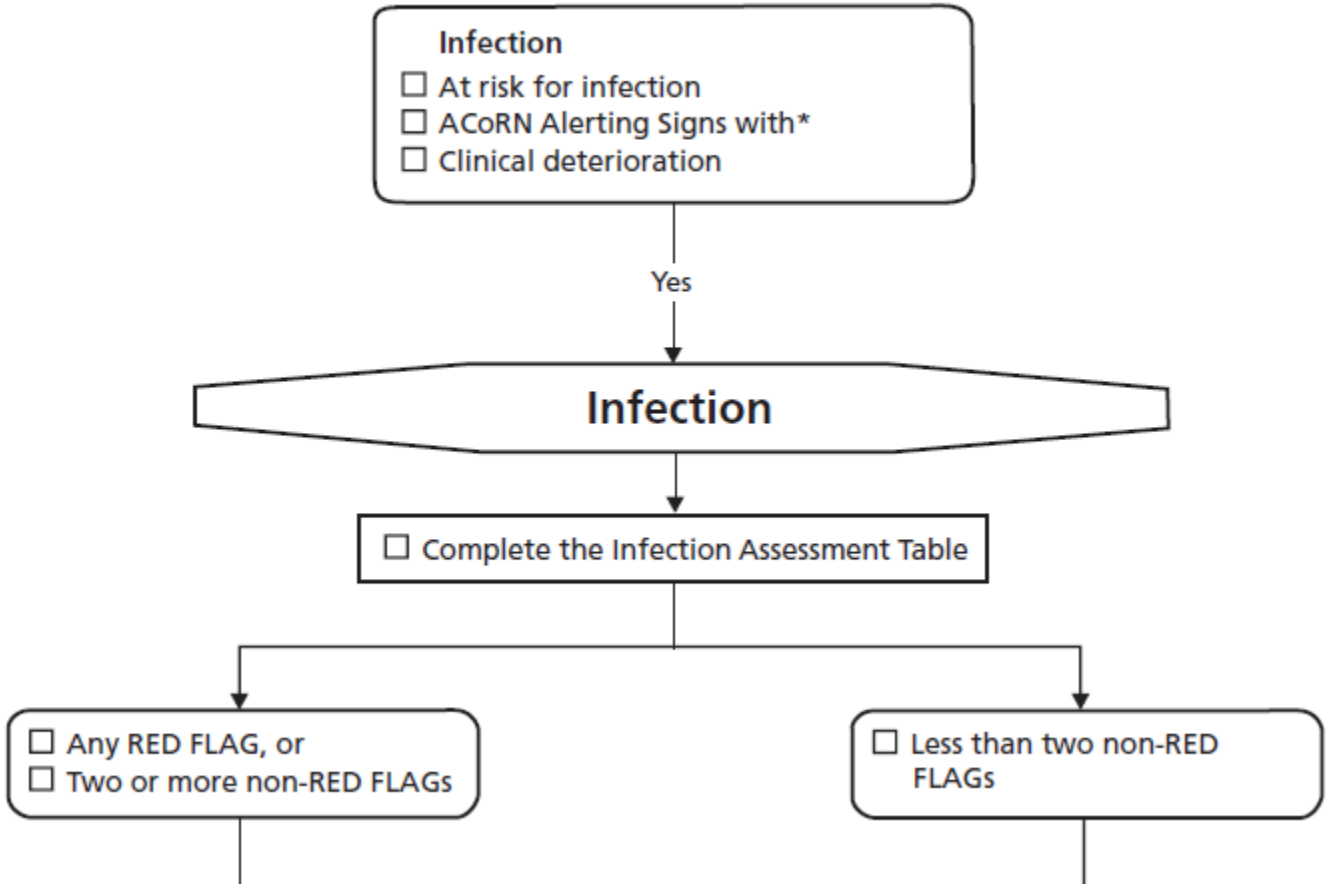
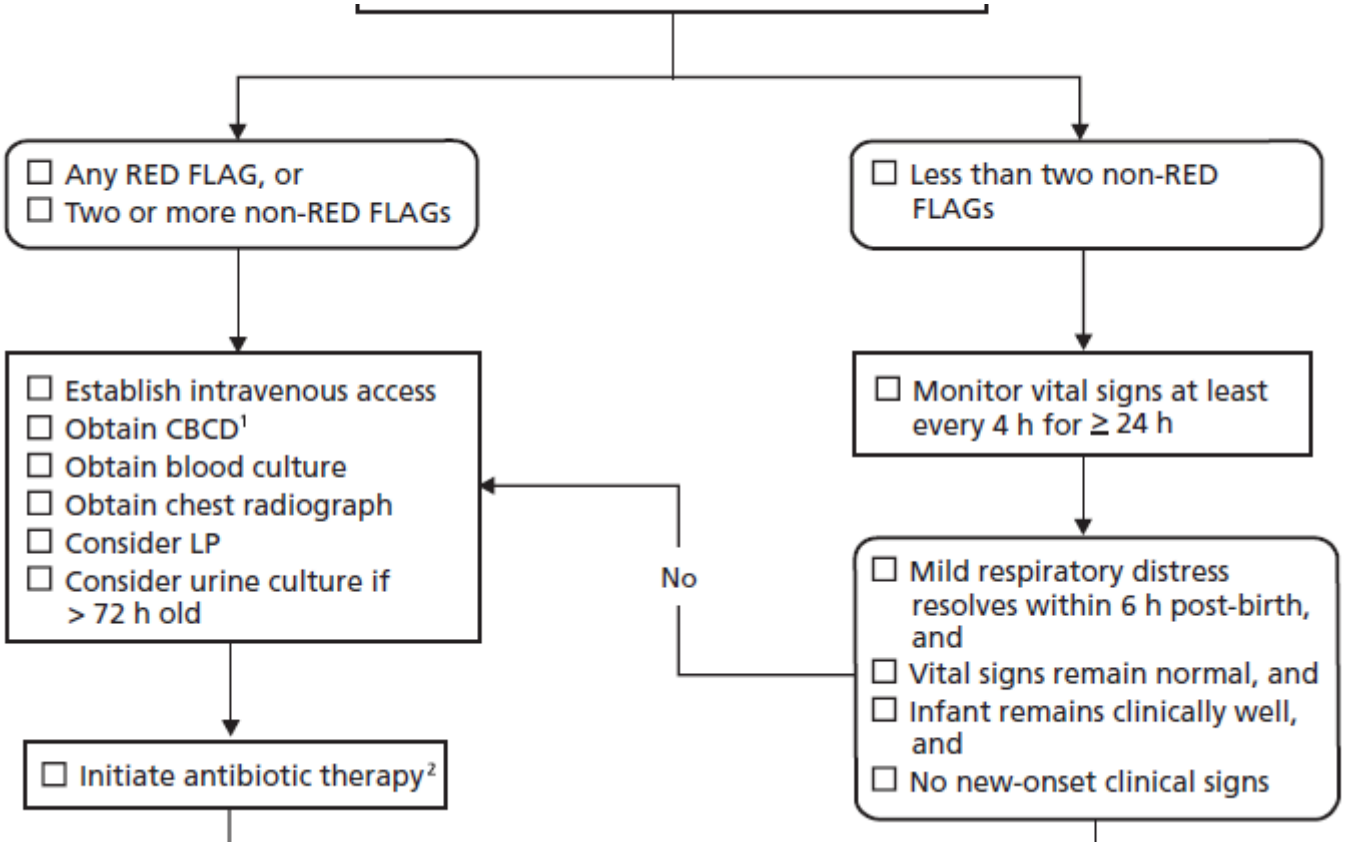



Infection
☐ At risk for infection
☐ ACoRN Alerting Signs with*
☐ Clinical deterioration
Yes
Infection
☐ Complete the Infection Assessment Table
☐ Any RED FLAG, or
☐ Two or more non-RED FLAGs
☐ Less than two non-RED FLAGs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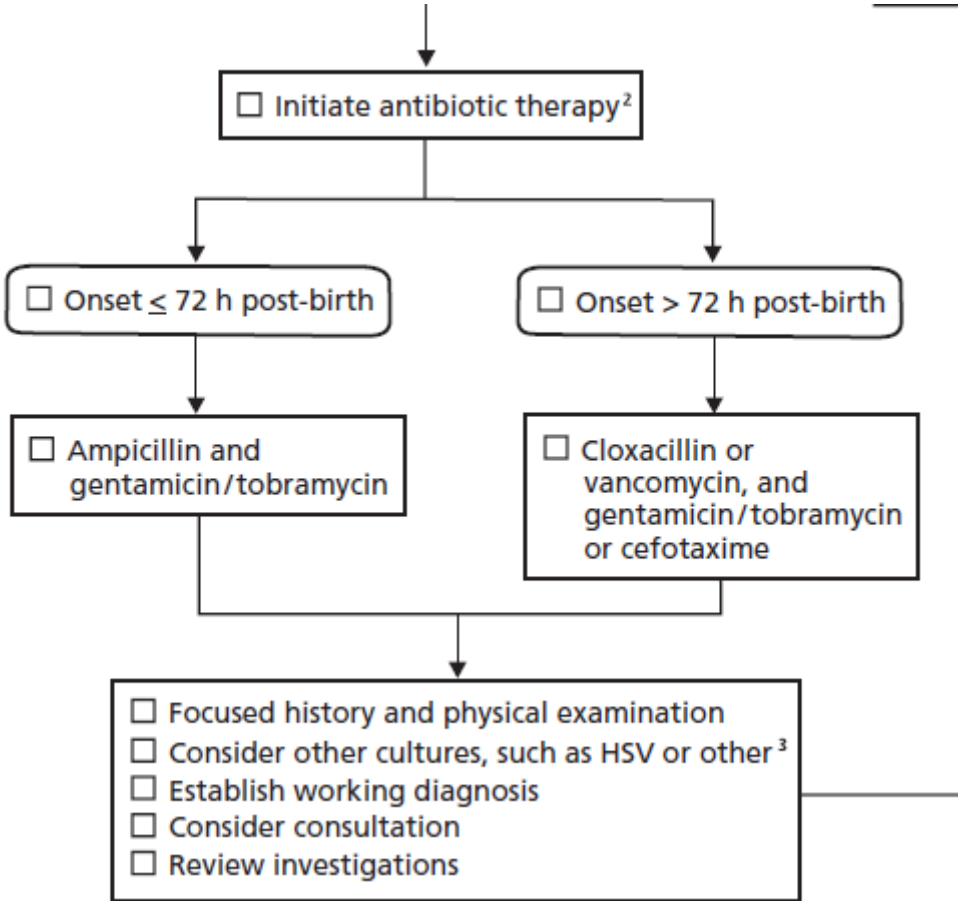
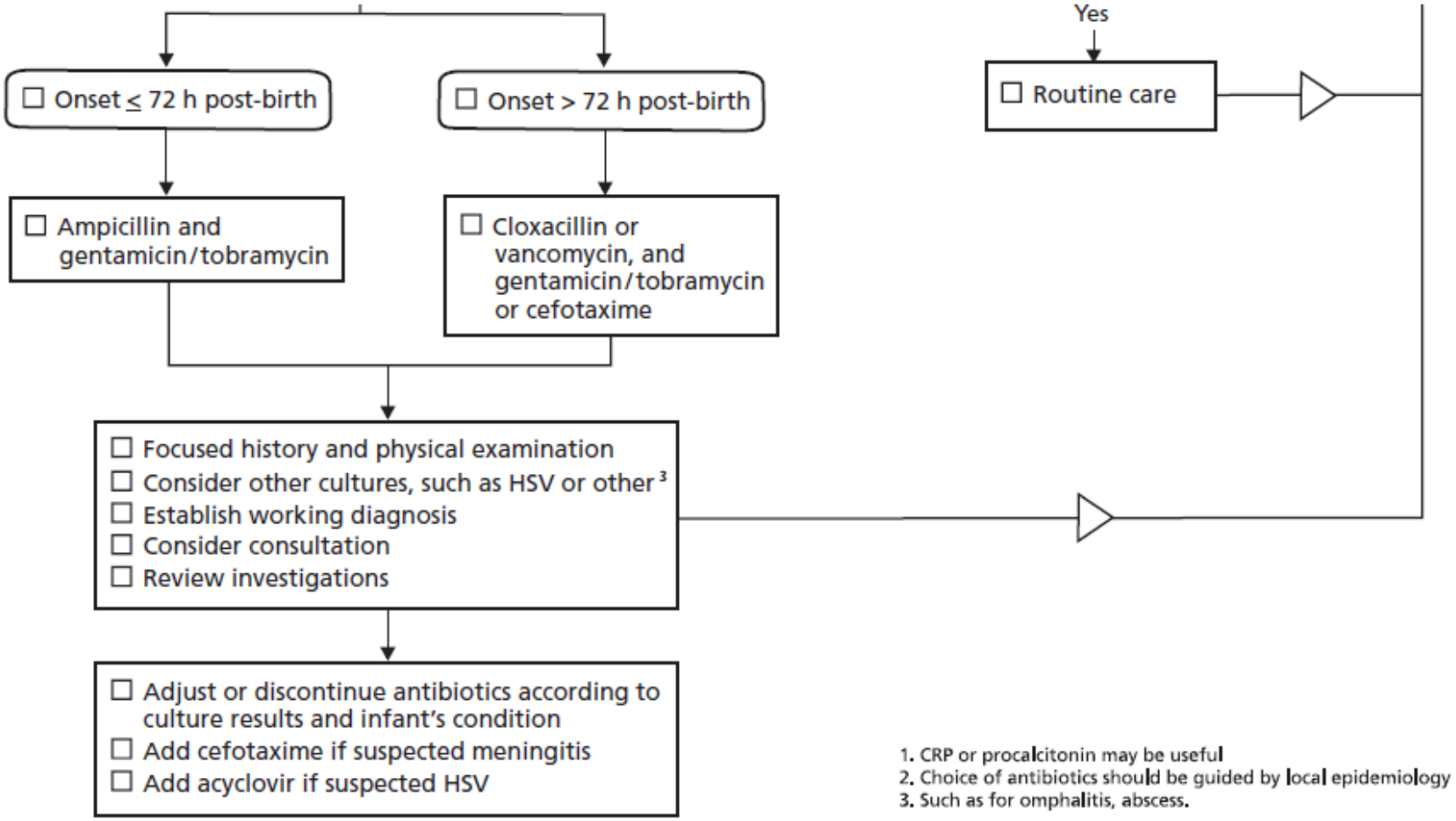
☐ Establish intravenous access
☐ Obtain CBCD[1]
☐ Obtain blood culture
☐ Obtain chest radiograph
☐ Consider LP
☐ Consider urine culture if > 72 h old
☐ Monitor vital signs at least every 4 h for ≥ 24 h
No
☐ Mild respiratory distress resolves within 6 h post-birth, and
☐ Vital signs remain normal, and
☐ Infant remains clinically well, and
☐ No new-onset clinical signs
☐ Initiate antibiotic therapy[2]


☐ Initiate antibiotic therapy[2]
☐ Onset ≤ 72 h post-birth
☐ Onset > 72 h post-birth
☐ Ampicillin and gentamicin/tobramycin
☐ Cloxacillin or vancomycin, and gentamicin/tobramycin or cefotaxime
☐ Focused history and physical examination
☐ Consider other cultures, such as HSV or other[3]
☐ Establish working diagnosis
☐ Consider consultation
☐ Review investigations

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3. Such as for omphalitis, abscess.

## *At risk for infection*

Specific risk factors for sepsis may be identified in the antenatal period, during labour, or after birth. Maternal risk factors associated with bacterial EOS in newborns are:

- GBS colonization during the current pregnancy,
- GBS bacteriuria during the current pregnancy,
- A previous infant with invasive GBS disease,
- PROM greater than or equal to 18 h before delivery,
- Prelabour rupture of membranes,
- Preterm birth (before 37 weeks GA) following spontaneous onset of labour,
- Intrapartum maternal fever (temperature greater than or equal to 38°C),
- Chorioamnionitis, and
- Suspected or confirmed invasive bacterial infection in the mother, treated during labour or in the 24-h-period before or after delivery.

- Suspected chorioamnionitis:
  - Maternal fever (two oral temperature readings of 38°C to 39°C at least 30 min apart *or* one oral temperature greater than 39°C) ***plus***
  - Any one of the following:
    - Baseline fetal heart rate greater than 160 bpm for 10 min or longer
    - Maternal WBC greater than $15 \times 10^9$/L
    - Purulent fluid from the cervical os.

- Definite chorioamnionitis:
  - ALL of the previously listed signs ***plus***
  - At least one of the following laboratory findings of infection:
    - Positive Gram stain of amniotic fluid
    - Low amniotic fluid glucose
    - High amniotic fluid white count
    - Positive amniotic fluid bacterial culture
    - Placental and/or fetal membrane histopathology with diagnostic features of inflammation and/or infection.

Risk factors associated with LOS in the neonate include:

- Low birth weight,
- Prematurity,
- Admission to an intensive care unit or special care nursery,
- Mechanical ventilation,
- Invasive procedures, and
- Invasive therapies (particularly indwelling IV catheters and endotracheal or chest tubes).

## *ACoRN Alerting Signs identified with**

Alerting Signs with an asterisk (*) are recognized clinical signs that may indicate sepsis. They include:

- Respiratory Sequence:
  - Laboured respirations
  - Respiratory rate > 60/min
  - Receiving continuous positive airway pressure (CPAP) or ventilation
- Cardiovascular Sequence:
  - Pale, mottled, grey
  - Weak pulses or low blood pressure
- Neurology Sequence:
  - Abnormal tone or activity
  - Abnormal level of alertness
  - Abnormal movements
- Thermoregulation Sequence:
  - T < 36.5°C or > 37.5°C axillary

## *Clinical deterioration*

Clinical deterioration in a previously well infant or worsening condition in an unwell infant is an indicator of possible sepsis and requires entry into the Infection Sequence.

Possible indicators of clinical deterioration include:

- Temperature instability. Sepsis can present with hypothermia, hyperthermia, or labile temperature control. Persistent high temperatures (greater than 38.5°C in infants, especially in the first week of life, may indicate a viral infection (e.g., herpes simplex virus [HSV]).
- Onset of apnea.
- Feeding problems (poor feeding, vomiting, excessive gastric aspirates, or abdominal distension).
- Metabolic abnormalities (hyper- or hypoglycemia, or metabolic acidosis with base deficit greater than 10).

## Infection Assessment

| Risk factors | | Clinical indicators | |
|---|---|---|---|
| **Red flag** | **Non-red flag** | **Red flag** | **Non-red flag** |
| ☐ Invasive maternal infection requiring IV antibiotic therapy 24 h before or after birth<br>☐ Infection in co-twin (multiple pregnancy) | ☐ Invasive GBS in previous infant and inadequate IAP<br>☐ Maternal GBS colonization or UTI in current pregnancy and inadequate IAP<br>☐ Rupture of membranes > 18 h<br>☐ Intrapartum maternal fever (> 38°C) or confirmed or suspected chorioamnionitis<br>☐ Preterm (< 37 weeks) birth following spontaneous labour | ☐ New-onset respiratory distress[1]<br>☐ Term infant receiving ventilation<br>☐ Shock<br>☐ Seizures | ☐ Laboured respirations, respiratory rate > 60/min<br>☐ Preterm infant receiving ventilation<br>☐ New-onset apnea in a preterm infant[1]<br>☐ Abnormal tone or activity and/or abnormal level of alertness<br>☐ New-onset[1] feeding problems: feeding poorly, vomiting, excessive gastric aspirates, abdominal distension<br>☐ New-onset[1] metabolic abnormalities, such as hyper-/hypoglycemia or metabolic acidosis (BD ≥ 10 mmol/L)<br>☐ Bilirubin at treatment level before 24 h of age<br>☐ Axillary temperature < 36.5°C or > 37.5°C, unexplained by environmental factors<br>☐ Local signs of infection (eye, skin, umbilicus) |

## Organization of Care

In the ACoRN Infection Sequence, Organization of Care is determined by the presence and number of **red flags** and **non-red flags** in the Infection Assessment Table.

- Infants with **any red flag or 2 or more non-red flags** are considered at higher risk of sepsis, and require additional investigations and immediate management.
- Infants with **less than 2 non-red flags** and no red flags are at a lower risk for sepsis. They require close observation and clinical judgement to determine appropriate management.

## Response

### *Infants with any red flag or 2 or more non-red flags*

Infants in this category require immediate IV access, diagnostic testing, and antibiotic therapy as per the Infection Sequence.

There are no screening laboratory tests, including WBC indices and serum biomarkers, sensitive enough to preclude treatment of the unwell infant. Similarly, unwell infants must be investigated and treated regardless of maternal GBS status and IAP.

## *Laboratory and diagnostic tests*

### *Complete blood count with differential*

Septic infants frequently have abnormalities in the number or distribution of WBCs or in their platelet count. Various WBC indices (total WBC count, absolute neutrophil count, IG counts, and I:T ratio) are used to aid diagnosis of neonatal sepsis. However, while the predictive value of these tests improves with the hours post-birth, it remains low overall. A low WBC count (less than $5 \times 10^9$/L) or a low absolute neutrophil count (less than $1.5 \times 10^9$/L) are more likely to be associated with sepsis than an elevated I:T ratio (greater than 20% to 30%) or a high WBC count (greater than $30 \times 10^9$/L). For more information

### *Blood cultures*

A minimum sample volume of 1 mL should be placed into an aerobic culture bottle to optimize growth in low-colony-count sepsis. Multiple cultures drawn from different sites have not been shown to improve detection rates. Blood can be taken from a newly inserted catheter or by venipuncture or arterial puncture. Most infections in the neonatal/perinatal period are bacterial in origin. The causative agents and the antibiotic treatment of choice can change depending on the timing of presentation.

### *Radiographs (X-rays)*

A CXR should be obtained whenever respiratory signs or symptoms are present. When gastrointestinal signs are present, an abdominal radiograph (AXR) is suggested.

### *Lumbar puncture (LP)*

Although meningitis is uncommon in newly born infants, a small number may have meningitis when the blood culture is negative. The LP can be deferred when the infant is experiencing cardiovascular or respiratory instability, presenting with early respiratory signs only, or when a trained, experienced clinician is not available to perform the procedure. The LP must be performed if the infant has signs of encephalopathy or seizures, or if the blood culture is positive.

### *Urine culture*

A urine culture by catheter or suprapubic aspiration should be obtained in infants more than 72 h old. Urine culture is not necessary for younger infants because urinary tract infection is rare in newly born infants.

### *Cultures from other sites*

Consider cultures from other sites (e.g., vesicle, wound, fluid, stool) or viral/fungal cultures when clinically indicated.

### *Serum biomarkers*

Testing other serum biomarkers, including CRP and procalcitonin, may be useful when evaluating a neonate for sepsis. A single CRP is not helpful in diagnosing EOS in the newly born infant. Serial negative CRPs have a high negative predictive value for sepsis. Emerging evidence suggests that procalcitonin may be a better marker than CRP for EOS in the neonate.

## *Antibiotics*

### *EOS*

In EOS, the most likely organisms are those acquired from the maternal gastrointestinal or genitourinary tracts. These include GBS, other streptococci (e.g., *S. viridans*), *Listeria monocytogenes*, and enteric gram-negative organisms like *E. coli*, *Klebsiella*, and *Enterobacter* species. First-line antibiotics for these organisms are ampicillin and an aminoglycoside (gentamicin or tobramycin). Initial antibiotic choice may be modified if maternal cultures and sensitivities are known.

**Table 10.2.**
**Common bacterial organisms in neonatal infection**

| Early-onset sepsis | Late-onset sepsis |
|---|---|
| Gram-positive bacteria<br>• *Streptococcus agalactiae* (GBS)<br>• *Listeria monocytogenes* | Gram-positive bacteria<br>• *Streptococcus agalactiae* (GBS)<br>• *Streptococcus pneumoniae*<br>• *Staphylococcus aureus**<br>• Coagulase-negative *Staphylococcus* species*<br>• *Enterococcus species** |
| Gram-negative bacteria<br>• *Escherichia coli (E. coli)*<br>• *Klebsiella pneumoniae*<br>• *Enterobacter species*<br>• *Proteus* species<br>• *Salmonella* species | Gram-negative bacteria<br>• *Escherichia coli (E. coli)*<br>• *Klebsiella pneumoniae*<br>• *Enterobacter* species<br>• *Proteus* species<br>• Other (*Citrobacter, Serratia, Pseudomonas, Haemophilus,* |

*Indicates organisms more commonly associated with nosocomial infections

### *LOS*

Organisms likely to cause LOS can differ depending on whether a neonate is being cared for in a NICU or special care nursery (hospital-acquired) or at home (community-acquired). In LOS, gram-positive organisms predominate, with coagulase-negative *Staphylococcus* infections accounting for one-half of all cases. Other organisms implicated in late-onset bacterial sepsis include GBS, *Staphylococcus aureus*, enterococci, other streptococci (e.g., *S. pneumonae*), *E. coli, Klebsiella* species, and *Pseudomonas* species.

First-line antibiotics for LOS are cloxacillin or vancomycin with an aminoglycoside (gentamicin or tobramycin) or cefotaxime. The initial choice of antibiotics may be modified depending on local microbiograms and sensitivity patterns.

## *Focused physical examination*

In general, EOS is usually characterized by respiratory distress, apnea, signs of distributive shock, pneumonia, and meningitis. LOS commonly presents with temperature instability, decreased activity levels, apnea, poor feeding, jaundice, and signs of distributive shock. Additional signs and symptoms may point to infections or complications in a particular organ system:

- Pneumonia: Respiratory distress, cyanosis responsive to oxygen, abnormal CXR
- Hematological: Petechiae from low platelet count or disseminated intravascular coagulation
- Meningitis: Seizures, high-pitched cry, bulging fontanels
- Gastrointestinal: Abdominal distension or discolouration, bilious vomiting, blood in stools

### *Infants with less than 2 non-red flags*

Infants in this category present with either a single risk factor for neonatal infection or one nonspecific symptom and no known risk factors. These infants require close monitoring because 95% of infants with EOS demonstrate symptoms within 24 h regardless of maternal IAP coverage. Vital signs should be monitored at least every 4 h over the next 24 h to ensure early recognition and management of infection.

Persistence of mild respiratory distress beyond 6 h of age in a newly born infant, abnormality in vital signs, clinical deterioration, or new-onset clinical signs during the monitoring period require a shift in the Organization of Care to the treatment arm, as per the Infection Sequence.

### *Consider other cultures*

Local site cultures (e.g., swabs or aspiration) may be warranted.

### *Establish a working diagnosis*

A working diagnosis is based on the timing of onset and suspected location of infection.

### *Consider consultation and review investigations*

To help direct specimen collection and additional management, consult with your referral centre. Review investigations as they become available, to help identify the source of infection and optimize antibiotic therapy.

## Specific Diagnosis and Management

When establishing a diagnosis, the clinician must consider whether an infection is localized to a specific organ or tissue (e.g., pneumonia, meningitis, urinary tract infection) or involves the bloodstream. Risk factors for unusual organisms or non-bacterial sepsis must also be considered. Although bacterial infection is the most common cause of neonatal sepsis, viral and fungal infections must be considered.

### *Bacterial sepsis*

Suspected bacterial sepsis is treated with broad-spectrum antibiotics until results from Gram stain and cultures are known. Antibiotic therapy should be modified to optimize treatment, depending on the

### *Viral sepsis*

Viral infections, particularly those caused by HSV or enteroviruses, should be considered if there is a history of recent maternal infection, active vaginal lesions, or diarrhea at the time of birth. Vesicular lesions on mother or infant should be investigated for HSV, but diagnosis does not depend on the presence of vesicles, which are absent in about 50% of cases.

HSV infection should be suspected in infants younger than 4 weeks of age with signs of CNS infection, persistent fevers, or clinical sepsis that does not respond to antibiotics, even when maternal history or symptoms are absent.

Treatment with acyclovir should be initiated urgently when HSV infection is suspected, especially in the presence of high fevers or neurologic signs.

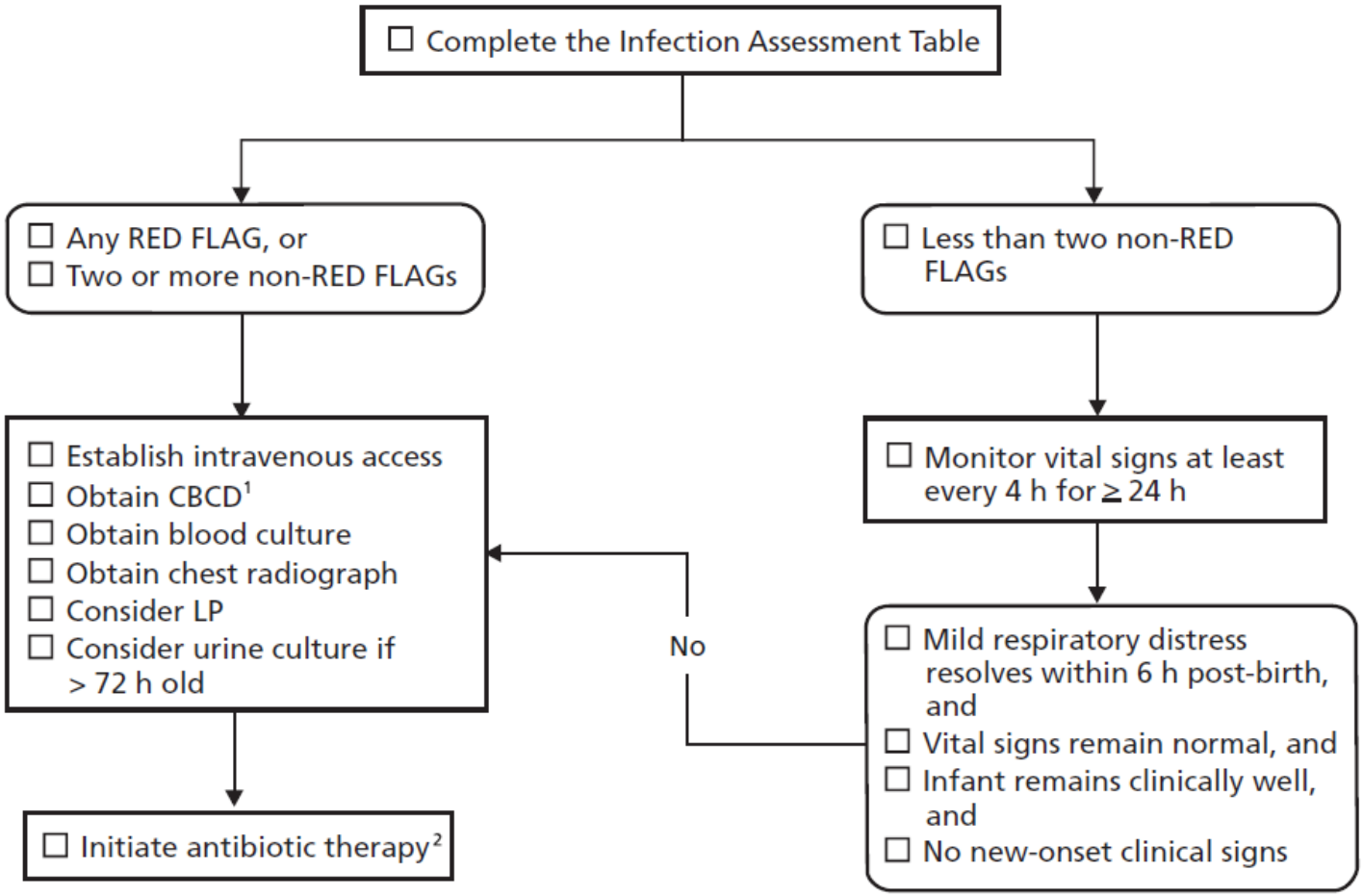
### *Fungal sepsis*

Fungal (most commonly *Candida*) infections may be vertically acquired from a maternal vaginal infection, but they are more often late-onset, nosocomial infections. Risk factors for invasive fungal infection include recent or prolonged broad-spectrum antibiotic use, known colonization of the skin or mucous membranes, and endotracheal tube use. Treatment of invasive fungal infections is beyond the scope of ACoRN.

## Infection: Case 1—A term infant with mild respiratory distress

*A baby girl is born in the operative birthing room. She is 30 min old. She was born by Caesarean section at 38 weeks for breech presentation approximately 60 min after the onset of contractions. Her mother has been healthy with no fevers. The GBS swab was negative, and membranes were intact at the time of delivery.*

*She is lying flexed skin-to-skin on dad's chest. She is grunting occasionally with mild subcostal retractions and a respiratory rate of 65 breaths/min. She is pink in room air.*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☐ Initiate antibiotic therapy[2]

Thirty min later, you reassess the baby.

*Her HR is 140 bpm and her respiratory rate is now 58 breaths/min, with a decrease in grunting and an oxygen saturation of 98% in room air. She has gone to breast to attempt a latch. Her temperature is 37.2°C skin-to-skin with mom.*

You confirm that there are no additional risk factors for infection.

**3. What are your Next Steps? Tick all that apply.**

- ☐ Monitor vital signs at least q 4 h.
- ☐ Reassess if clinical deterioration OR respiratory distress persists > 6 h.
- ☐ Continue assessment using the Respiratory Score as long as respiratory distress persists and the infant is spontaneously breathing.
- ☐ Discharge home.
- ☐ Perform a complete blood count with differential and start antibiotics.