Late Onset Sepsis Prophylaxis and Treatment 2022

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Defined as infection that presents after 72 hours of life in a neonate. This is often applied to any infection prior to initial hospital discharge in VLBW infants. LOS is attributed to organisms acquired from the hospital or community. The most common causes of LOS are *Staphylococcus* species (Coagulase negative staphylococcus, *Staphylococcus aureus*), gram-negative bacteria (*Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Serratia* species, *Pseudomonas* species), *Streptococcus agalactiae* (GBS), *Enterococcus faecalis* and Candida species. The incidence of LOS is gestational age dependent, with infection rates as high as 50% in infants <1000 g. The survival of low birth weight infants has improved greatly in recent years, but the care of these infants involves procedures (endotracheal intubation, catheters, lines, broad-spectrum antibiotics) that increase their risk of nosocomial infection.

I. **Prophylaxis:**

a. IVIG

i. Rationale: Maternal IgG is the major source of fetal and neonatal IgG. Since significant transfer of maternal IgG across the placenta to the fetus does not begin until the 32nd week of gestation, VLBW (<1500 g) infants are born with relatively low levels of IgG compared with full-term infants. Furthermore, in all infants, serum immunoglobulin levels decline further after birth. In term infants, the postnatal physiologic trough occurs at 4 - 6 months of age, but serum IgG levels usually remain above 400 mg/dl. Preterm infants can have levels as low as 60 mg/dl by 3 months of age. Together, the increased risk factors for sepsis and the relative quantitative and qualitative IgG deficiency in preterm infants (that increases with postnatal age) provide a rationale for intravenous immunoglobulin (IVIG) therapy as a means for prophylaxis of neonatal sepsis. Individual clinical studies have failed to consistently demonstrate a beneficial effect of prophylactic IVIG in reducing the incidence of hospital-acquired infections in VLBW infants (Baker 1992; Fanaroff, 1994). However, several meta-analyses suggest a demonstrable benefit of prophylactic IVIG in preventing sepsis in LBW newborns (Jensen 1997, Ohlsson 2020).

ii. In preterm infants born < 26 weeks' gestation, we monitor a serum IgG level at birth and then every 1 week for the first 4 weeks. This monitoring can be extended based on the clinical course. If serum IgG level is < 200 mg/dl, we give IVIG 500 mg/kg IV as long as the infant has an indwelling IV line.

1. IVIG should be administered by itself, with careful monitoring during the infusion. Vital signs should be monitored during the infusion (preferably q 15 minutes X 2, then q hr). In the large multicenter trials involving infants, very few adverse reactions were noted during infusion. These consisted of mild increases or decreases in blood pressure, heart rate, or temperature (that were reversed by slowing the rate of infusion) or acute fluid overload. Since the dose of IVIG is equivalent to an approximately 10 ml/kg fluid bolus, the infusion is administered over several (typically 3 - 4) hours.
2. Whenever possible, we administer doses on Mondays to reduce cost by allowing multiple infants to be treated from the same vial of IVIG.

b. Probiotics

i. Rationale: Probiotic use has been shown by several systematic reviews and metanalyses to reduce the rate of LOS in LBW infants without significant evidence of harm (Zhang 2016, Aceti 2017, Dermyshi 2017). Additionally, using a combination of different probiotic strains, rather than a single strain, seems to offer the greatest benefit (Aceti 2017).

ii. We start probiotics on preterm infants ≥ 23 weeks' gestation who are ≥ 3 days of age and are receiving an enteral intake of ≥ 6 mL total per day.

1. We use Ultimate Flora (formerly FloraBABY, licensed health product Canada) probiotic mixture containing 4 Bifidobacteria (*Bifidobacterium breve*, *bifidum*, *infantis* and *longum*) and *Lactobacillus rhamnosus* GG at a concentration of 2 x 10^9 colony forming units per 0.5 g (Janvier 2014).

a. 500 mg of Ultimate Flora is added to 2 mL of D2.5W and is given once daily (usually in the evening) by NG/OG/PO before a scheduled feed. The probiotic species survive better if the liquid contains dextrose.
b. Probiotic doses are prepared daily by pharmacy to minimize the risk of contamination.
c. After giving a dose, the nurse will discard their gloves, perform hand hygiene and don new gloves before proceeding with cares.
d. Doses are held while infant is NPO, unless the attending physician recommends continuation.

2. Probiotics are typically discontinued when the infant reaches 36 0/7 weeks' post-menstrual age, but may be continued beyond this on a case-by-case basis.

c. Fluconazole

i. Rationale: The use of prophylactic fluconazole in VLBW infants reduces the rate of invasive fungal infections and is of greatest benefit in centers with high baseline fungal infection rates (Wang 2021, Anaraki 2021).

ii. We start fluconazole prophylaxis at birth in infants ≤ 24 weeks' gestation.

1. We give fluconazole 3 mg/kg IV q72 hours over 60 minutes through the first 14 days of life.

d. Vancomycin for central line removal

i. Rationale: The removal of central lines is associated with the development of LOS (van den Hoogen 2008). Preterm neonates who received a single dose of antibiotics within 12 hours of central line removal have decreased post-removal sepsis events (Reynolds 2015).

ii. A single dose of Vancomycin is given to neonates ≤ 3500 grams whose central line has been in place for > 7 days (PICC or UVC) and who has not received a dose of antibiotics in the previous 12 hours.

1. Vancomycin 15 mg/kg is infused through the central line that will be removed over 90 minutes. The peak serum Vancomycin concentration is reached approximately 30 minutes after the end of the infusion, so the central line is removed after the 30 minute post-Vancomycin flush is completed.

II. **Evaluation and Treatment**

a. Evaluation

i. We obtain weekly screening tracheal aspirates in all infants who are intubated or have a tracheostomy. We do not routinely treat the organisms in these aspirates, but do use them to guide antibiotic choices and duration if there is a concern for a ventilator-associated pneumonia or tracheitis.

ii. At the time of sepsis evaluation, we send a CBCPD, CRP, blood culture, urinalysis and urine culture. Risk factors, clinical presentation and post-menstrual age determine whether CSF studies, HSV studies and/or respiratory viral studies are included in the evaluation.

b. Treatment

i. To cover the most common organisms causing LOS (including multi-drug resistant *Pseudomonas* species), we start the following antibiotics when LOS is suspected:

1. Vancomycin 15 mg/kg IV

a. Dosing interval is based on post-menstrual age and time since birth

i. Q18h

1. PMA < 30 weeks and < 15 days of age

ii. Q12h

1. PMA < 30 weeks and > 14 days of age
2. PMA 30-36 weeks and < 15 days of age
3. PMA 37-44 weeks and < 8 days of age

iii. Q8h

1. PMA 30-36 weeks and > 14 days of age
2. PMA 37-44 weeks and > 7 days of age

iv. Q6h

1. PMA > 44 weeks

b. We check a trough level before the 2nd dose if PMA < 30 weeks or before the 3rd dose if PMA > 30 weeks with a goal level of 5-10 μg/ml and adjust the interval accordingly

2. Gentamicin
   a. Dosing based on post-menstrual age and time since birth
      i. 5 mg/kg IV q48h
         1. PMA < 30 weeks and < 8 days of age
      ii. 4 mg/kg IV q36h
         1. PMA < 30 weeks and 8-28 days of age
         2. PMA 30-34 weeks and < 8 days of age
      iii. 4 mg/kg IV q24h
         1. PMA < 30 weeks and > 28 days of age
         2. PMA 30-34 weeks and > 7 days of age
         3. PMA ≥ 35 weeks
   b. Peak and trough levels per pharmacy recommendations
3. Zosyn 100 mg/kg IV
   a. Dosing interval based on post-menstrual age and time since birth
      i. Q12h
         1. PMA < 30 weeks and < 29 days of age
         2. PMA 30-36 weeks and < 15 days of age
         3. PMA 37-44 weeks and < 8 days of age
      ii. Q8h
         1. PMA < 30 weeks and > 28 days of age
         2. PMA 30-36 weeks and > 14 days of age
         3. PMA 37-44 weeks and > 7 days of age
         4. PMA > 44 weeks

ii. Antibiotics are tailored after 48 hours based on clinical picture, laboratory and culture results

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