

Intensive Care Nursery House Staff Manual

Candidiasis in the Newborn

DEFINITIONS: Candidiasis refers to infection with fungi of the genus *Candida*. Candidemia is presence of *Candida* fungi in the blood. Catheter-related candidemia refers to candidemia that resolves rapidly after catheter removal and initiation of therapy. Disseminated, or invasive, candidiasis refers to persistent infection after removal of a catheter and/or isolation of *Candida* from other normally sterile body sites.

EPIDEMIOLOGY: Invasive candidiasis in neonates is a serious and common cause of late onset sepsis and has a high mortality (25 to 35%). The incidence of such fungal infections has increased 11 fold over the past 15 years. *Candida* species are the 3rd most frequent organism (after coagulase negative *Staph.* and *Staph. aureus*) isolated in late-onset sepsis in very low birth weight (VLBW) infants (*i.e.*, <1,500 g). Preterm infants are predisposed to *Candida* infections because of immaturity of their immune system and invasive interventions. Transmission of *Candida* may be vertical (from maternal vaginal infection) or nosocomial. Colonization of health workers is as high as 30%. Initial site of colonization is usually the gastrointestinal tract. Risk factors for candidiasis include: a) low birth weight (<1,500 g); b) use of broad spectrum and/or multiple antibiotics; c) central venous catheters; d) parenteral alimentation and intravenous fat emulsion; e) colonization with *Candida* and/or previous episode of mucocutaneous candidiasis; f) prolonged urinary catheterization. Although initial reports indicated most cases were due to *Candida albicans*, more recent studies show emergence on non-*albicans* species including *C. parapsilosis* (cause of majority of cases in some centers), *C. glabrata*, *C. krusei*, *C. lusitaniae* and *C. tropicalis*.

CLINICAL MANIFESTATIONS: The classic clinical picture of systemic candidiasis in neonates is indistinguishable from bacterial sepsis. Common presenting symptoms are **worsening respiratory function, apnea, thrombocytopenia** and **localized signs of candidal infection** at one or more of the following sites:

- Skin and mucous membranes** (thrush, diaper rash or other areas)
- Central nervous system:** Meningitis is present in up to 64% of fatal cases, and survivors have a high incidence of severe sequelae including hydrocephalus, psychomotor and mental retardation, and aqueductal stenosis
- Eyes:** Fundoscopic examination is essential for early diagnosis of invasive disease, as the incidence of *Candida* endophthalmitis is as high as 50%.
- Heart:** *Candida* endocarditis is the 2nd most common form of endocarditis in VLBW infants. Clinical findings may include cardiac murmurs, petechiae, skin abscesses, arthritis, hepatomegaly and splenomegaly. Right-sided intracardiac fungal masses can manifest with heart failure or even with pulmonary fungal embolism.
- Kidneys:** *Candida* is the most frequent cause of urinary tract infection in intensive care nurseries. Up to 50% of these babies have candidemia and are predisposed to renal candidiasis, with development of renal fungus balls or abscesses and unilateral or bilateral renal obstruction. Renal insufficiency may be the first clinical manifestation of invasive candidiasis.

-Bones and Joints: Warmth and swelling of the extremities in combination with radiographic evidence of osteolysis or arthritis.

Congenital Candidiasis: A rare entity in which intrauterine infection is evident at birth. Two forms have been described:

- 1) **Congenital cutaneous candidiasis** in which an extensive skin rash presents within 12 hours of birth. A macular erythema that may evolve from a pustular, papular or vesicular phase finally results in extensive desquamation.
- 2) **Congenital systemic candidiasis:** An invasive infection with a high mortality rate, especially in VLBW infants. At least 50% do not have a cutaneous rash. Presenting signs are pneumonia (most common), meningitis, candiduria and/or candidemia.

DIAGNOSIS: Consider *Candida* in the differential diagnosis of neonatal sepsis, particularly late-onset. When **blood culture is positive for *Candida***, a thorough evaluation to rule out **disseminated infection** should include **cultures of urine and CSF, ophthalmological examination, echocardiogram, renal ultrasound** and, if clinical signs of arthritis or osteomyelitis are present, **radiographic skeletal survey and consider diagnostic aspiration of affected area.**

TREATMENT: Remove central venous catheter, unless blood stream infection clears rapidly with antifungal therapy.

Amphotericin B, the gold standard for neonatal antifungal therapy, exerts its mechanism of action and toxicity through binding to ergosterol in the cell membrane of fungal and host cells, resulting in formation of membrane pores, cell depolarization followed by cell death. Side effects include nephrotoxicity, hypokalemia, hypomagnesemia, anemia, thrombocytopenia and infusion reactions (temperature and hemodynamic instability).

Liposomal Amphotericin B allows targeted antifungal therapy with less toxicity. The drug is cleared through the reticuloendothelial system allowing higher liver and spleen concentrations and reduced renal concentrations.

Flucytosine (5-FC) interferes with DNA synthesis. Because of toxicity and development of resistant strains, it is of limited use in neonatal infections. However, if the infant can tolerate oral medications, flucytosine is very useful for CNS infections and may act synergistically with amphotericin B.

Fluconazole, a fungistatic drug, is the most effective of the azoles. Hepatotoxicity, the main side effect, is transient and resolves with cessation of therapy. It has decreased activity against *C. glabrata* and *C. krusei*.

Consultation with the Infectious Disease Service should be obtained for all neonatal fungal infections except those limited to skin and mucous membranes.