QUICK LESSON

Candidiasis, Invasive Neonatal

Description/Etiology

Invasive neonatal candidiasis is a life-threatening systemic infection caused by yeast of the genus *Candida*; it particularly affects preterm neonates(CDC).Prematurity lends itself to immunosuppression, and admission to the NICU is associated with a number of risk factors that can contribute to candidiasis (King). The condition is associated with high morbidity and mortality rates, multi-organ failure, longer hospital stays, and increased costs for both patients and healthcare facilities (CDC, Ramos, Pappas).

Among the most common causative pathogens of candidiasis are *C. parapsilosis, C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. krusei* (CDC, Dalal, Pappas). Infection can be acquired in the perinatal period, especially in cases of vaginal delivery or when a mother has chorioamnionitis and/or *Candida* found in the placenta (Barton). It can also be acquired following colonization in the hospital environment (Dalal). The most common form of invasive candidiasis occurs in the bloodstream (i.e., candidemia), but it can also occur in the heart, brain, eyes, bones, kidneys, and other organs without bloodstream involvement (CDC, King).

Early diagnosis coupled with prompt and adequate treatment of invasive candidiasis is associated withless severe disease course and improved outcomes (Kaufman).However, diagnosis is often delayed because the infection presents with nonspecific clinical features that are indistinguishable from those of bacterial infection, andthe abilities of blood cultures or biopsies to diagnose fungal infections are poor. The condition should be suspected in preterm neonates with persistent symptoms of infection despite antibiotic therapy. Diagnosis is achieved by isolating*Candida* from samples of blood, tissue, or fluid from infected sites of the body (CDC).

Neonatal invasive candidiasis can be cured with antifungal medications (e.g., fluconazole, amphotericin, echinocandins)(CDC, Pappas). Because diagnosis is often delayed and the condition is associated with a high risk for severe and long-lasting/permanent adverse effects (e.g., endophthalmitis, endocarditis, neurodevelopmental impairment, organ abscesses) and death, prevention is an important goal. High-risk neonates can be treated prophylactically with antifungal medications (e.g., fluconazole, or Nystatin as a second-line prophylactic) (CDC, Pappas).

Facts and Figures

Candida is a leading cause of healthcare associated bloodstream infections in some developed countries, and the leading cause of invasive fungal infections among children in hospitals, however the prevalence of candidemia specifically in neonates has fallen over time (CDC, Walsh). *Candida* infections may occur as often as 29.6 episodes per 100,000 NICU inpatient days (Hsu). As many as 21% of all NICU patients may be colonized with *Candida* (Dalal).

Candida infections represent one of the major causes of infection-related deaths in the NICU (Dalal). Neonatal invasive candidiasis is associated with an18-44% mortality rate even with appropriate therapy,and a 33% rate of neurodevelopmental impairmentamong survivors (e.g., cerebral palsy, psychomotor deficits, blindness, hearing loss) (Ramos, Autmizguine, Ezenwa).

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As many as 31% cases of invasive candidiasis among extremely low birth weight (ELBW) neonates present as an early onset (i.e., in the first 7 days of life); early onset invasive candidiasis tends to have poorer outcomes and higher mortality than later onset cases (Barton). Among neonates with early onset invasive candidiasis, as many as 80% will die or have permanent neurological impairments; 72% will die or have permanent neurological impairments among late-onset cases (Barton).

Risk Factors

Risk factors include prematurity and low birth weight, previous resuscitation, maternal cervical devices in place (e.g., intrauterine device, cerclage), treatment with broad-spectrum antibiotics, proton-pump inhibitor administration, pre-existingchronic lung disease or pulmonary hypertension, prolonged dependence on TPN/hyperalimentation, prolonged ICU admission, pre-existing neurological issues, immunodeficiencies, corticosteroid administration, recent invasive procedures/surgeries, indwelling catheters, abdominal surgery, necrotizing enterocolitis, and colonization with*Candida*(CDC, Dalal, Ramos, Pappas, King, Hsu, Ezenwa, Barton, Kaufman). Candidemia is noted to be twice as high among Black people as compared to non-Black people (CDC).

Early onset of invasive candidiasis may occur more often in female neonates, those born prior to 24 weeks gestation, weighing less than 750 grams, born via vaginal delivery, and/or born to mothers with chorioamnionitis (Barton).

Treatment failure has been noted to occur at higher rates among infants with septic shock, delayed removal of infectious medical devices (e.g., central venous catheters), pre-existing renal disease, or breakthrough invasive candidiasis (Hsu).*Candida* infections noted in the urine have a very high fatality rate among ELBW neonates; survivors are likely to have neurodevelopmental delays or anomalies (Pappas).

Signs and Symptoms/Clinical Presentation

Infection may developas soon as 3 days after birth if the cause is congenital (Ezenwa). Clinical signs may be subtle and nonspecific, and can include respiratory deterioration (e.g., apnea, requiring use of respiratory support), tachycardia, enteral feeding intolerance, skin lesions (e.g., pustules, excoriations, erythema, diffuse maculopapular rash, peeling/scaling), body aches, hyperglycemia, vision symptoms (chorioretinal or vitreous lesions), fever, and hypotension (Ramos, Pappas, Walsh, Barton, Kaufman).

Symptoms may be reflective of the area of the body affected by the fungus (CDC). Hepatosplenic involvement may cause abdominal pain and anorexia (Walsh). Renal involvement may manifest as creatinine clearance issues, renal bezoars (i.e., stony concentrations), or obstructive nephropathy (Walsh). Haematogenous*Candida* meningoencephalitis (HCME) occurs when *Candida* invades the meninges and causes seizures, intraventricular hemorrhages, developmental regression or delays, and an increase in nucleated cell count (i.e., pleocytosis) in the CSF (Walsh). Endocarditis secondary to invasive candidiasis is not common among neonates, but is associated with heart murmur, peripheral emboli, and/or symptoms of congestive heart failure (Pappas, Walsh, Barton).

Assessment

› **Patient History**
- Assess for risk factors,especially in those born prematurely and/or with low birth weight (CDC, Dalal, Ramos)

› **Physical Findings of Particular Interest**
- See *Signs and Symptoms/Clinical Presentation*, above

› **Laboratory Tests That May Be Ordered**
- Isolation of *Candida* from cultures/biopsies of blood, urine, sterile bodily fluids (e.g., peritoneal fluid, CSF) and/or tissues (e.g., skin)is diagnostic of invasive candidiasis(CDC, Ramos, Yuan, Kaufman).
  - Blood culture results for neonates may be a poor diagnostic tool for candidemia, as it requires larger blood volumes than may be feasible to attain (Ramos, Ezenwa)
  - Placental culture may also be useful if symptoms of early onset candidiasis occur (Kaufman)
- Staining of the placenta or umbilical cord in suspected cases of cutaneous congenital candidiasis may identify inflammation (Kaufman)
- CBC can reveal thrombocytopenia (Ramos, King)
- Electrolyte/chemistry panels and/or blood gases can reveal metabolic acidosis and hyperglycemia (Ramos)
  - Elevated BUN may be associated with nephrotoxicity secondary to AmB administration (Yuan)

› **Other Diagnostic Tests/Studies**
- Radiological studies including ultrasound, CT scan, and echocardiogram will identify organ involvement, if present; these should be considered especially if serial blood cultures continue to show *Candida* infection during antifungal treatment course (Ramos, Pappas)
  - Abscesses may develop on the liver, spleen and kidneys (Autmizguine)
  - Infective endocarditis can occur (King)
- Dilated retinal examination to assess for endophthalmitis if blood/urine is the positive source of *Candida* (Pappas, Autmizguine)
- Lumbar puncture if blood/urine is the positive source of *Candida* (Pappas)

Treatment Goals

› **Promote Optimum Physiologic Function and Monitor for Complications**
- Monitor vital signs, all physiologic systems, and laboratory results per facility protocol; report abnormalities and treat as prescribed
  - Consider discontinuation of humidified air into isolettes for extremely premature patients who present with skin symptoms (Kaufman)
- Administer antifungal medications, as ordered by the treating clinician; recommended duration of treatment is 14 days past a noted clearance of *Candida* from the blood in conjunction with resolved symptoms of *Candida* infection (Pappas);
  - First-line treatment may include AmB deoxycholate (Pappas)
    - Complications of AmB therapy include nephrotoxicity, electrolyte imbalances, and hepatotoxicity (Yuan, Silver)
    - Neonates tend to suffer less nephrotoxicity on AmB deoxycholate than older children and adults (Pappas, Silver)
    - Newer lipid formulations of AmBshould be used with caution in neonates due to limited data on CNS and renal penetration, especially if there is urinary tract involvement (Pappas,Silver)
    - AmB may be given intrathecally in cases of *Candida* meningitis (Yuan)
  - Fluconazole may also be used as a first-line treatment if it has not been previously been given for antifungal prophylaxis (Pappas)
  - Echinocandins may be considered in cases of drug toxicity or resistance to fluconazole or AmB; these should be used with caution (Pappas)
  - Flucytosine may be effective in neonates with CNS infections who are not responding to AmB, but there are many adverse effects to be cautious of in neonates (e.g., GI symptoms leading to poor feeding tolerance) (Pappas)
- Removal of implanted medical devices should be strongly considered(Pappas)
  - Central venous catheters should be removed promptly; replacement should occur in a different body site (Pappas)
  - CNS devices (e.g., ventriculostomy drains and shunts) will ideally be removed in the CNS is involved (Pappas)

› **Reduce Parental Anxiety, Educate, and Encourage Active Participation in Care**
- Assess parental anxiety level and coping ability; respond to questions/concerns and encourage expression of feelings; request referral, if appropriate, to a
  - mental health clinician for counseling support
  - social worker for identification of local resources (e.g., support groups)

Food for Thought

› In the United States, the Centers for Disease Control and Prevention (CDC) has worked with a portion of state health departments to track and monitor cases of candidemia in an effort to better understand risk factors, prevalence, and prevention strategies (CDC)
- Declining rates of candidemia among pediatric patients may be due to improvements in central venous catheter maintenance and insertion practices (Walsh)

› There is a need for rapid and sensitive testing to promote early diagnosis and treatment of invasive candidiasis; promising options include the beta-D-glucan assay, *Candida* PCR, and a combination diagnostic method of magnetic resonance technology coupled with nucleic acid amplification on serum blood draws (CDC, Ramos, Walsh)
- PCR testing is especially promising because of its short turnaround time for results and ability to utilize very small amounts of blood (Ramos)
- The magnetic resonance/nucleic acid amplification assay also has been shown to have rapid turnaround times within hours, but has not been studied in large groups of pediatric patients (Walsh)

› Though not typically associated with infectious outbreaks, a newly emerging *Candida* pathogen, *C. auris*, has caused outbreaks and is of concern due to its resistance to some antifungal agents and hospital disinfectants (CDC)

Red Flags

› Administration of AmB can be associated with life-threatening adverse effects, including renal failure or hypokalemia (Silver)
  • Other signs/symptoms to monitor for are polyuria, and elevated BUN and creatinine (Silver)
› Infective endocarditis secondary to invasive candidiasis may be more common in those patients with pre existing cardiac conditions; it should be considered if new onset fever and heart murmur, peripheral emboli, and/or symptoms of congestive heart failure are noted (King, Walsh, Barton)

What Do I Need to Tell the Patient's Family?

› Discuss the importance of parental bonding with the affected neonate
› Upon patient discharge, educate parents to seek immediate medical attention for new or worsening signs and symptoms
› If appropriate in severe cases, encourage family discussions of end-of-lifeissues
› Discuss with parents the importance of providing antifungal prophylaxis to prevent potentially life-threatening infection in high-risk neonates (CDC, Pappas)

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