INVASIVE FUNGAL INFECTION IN NEONATE

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Abstract

Technological advances in recent decades have enabled significant and improving results in the care of newborns, especially those with extremely low birth weight. However, these strategies have also facilitated an increase in fungal infection or colonization, such as hospitalization in intensive care units and the use of various medical procedures. Fungal infection present with a variety of clinical course, from mild mucoutaneus infection to life-threatening invasive fungemia, and leads to poor neurodevelopmental outcome.

Candida species are a major cause of invasive fungal infection and the third most-common cause of late onset sepsis in critically ill neonates, especially very low birth infant and extremely low birth infant. Numerous risk factors have been identified. The high morbidity rate related to invasive candidiasis leads to the consideration of empirical antifungal therapy and prophylactic approaches for infants at high risk. Infection control as well as anti-fungal prophylaxis can decrease the incidence and severe morbidity.

Introduction

Fungi can be found free-living in the soil, on bird and mammalian feces, and in decaying organic matter as well as in the hospital environment. Candida, one of fungi species which reported as the most common cause of invasive fungal infection (IFI) in neonate, are commensal organism in the human oral cavity, gastrointestinal tract, genitourinary tract, and moist intertriginous skin folds. Neonates can acquire the organism as vertically transmission from the mother during passage through the birth canal and in utero from hematogenous spread or ascending vaginal infection. They can also acquire the infection post-natally through inhalation, ingestion, direct inoculation into the skin, and exposure to the hospital environment. (Sims 2008)

Invasive fungal infection (IFI) refers to persistent infection after removal of a catheter and/or isolation of fungus from other normally sterile body sites (blood, cerebrospinal fluid, and urine collected by suprapubic sterile puncture or sterile bladder catheterization, with a grow of >10.000CFU/ml) of an infant with clinical signs of infection (Montagna 2010).

Since Candida is the most–common cause of IFI in neonate, this article will be focus on invasive Candida infection (ICI).

Epidemiology:

Candida spp is the third most-common cause of late onset sepsis in critically ill neonates, especially very low birth infant (1001-1500 g, VLBW) and extremely low birth infant ≤1000 g, ELBW) (Benyamin DK, 2006) with an incidence ranging from 2.6 to 10% among VLBW (Levy 2006) and from 5.5 to 20% among ELBW (Chapman RL 2007, Benyamin DK, 2006,) . Although invasive candidiasis began to decrease in 2001 (Aliaga 2012), The mortality rate is as high as 25 to 60%. (Benyamin 2006).

Seven of more than 100 species of candida are well known pathogens in humans (Sims 2008) . Although initial reports indicated most cases were due to Candida albicans, more recent studies show emergence on non-albicans species including C. parapsilosis, C.glabrata, C. krusei, C.lusitaniae and C.tropicalis. (Makhoul 2001, Roilides 2002, Ariff 2011))

Transmission of candida may be vertical (from maternal vaginal infection), or nosocomial. Candida colonization may be acquired by the fetus during gestational development or at delivery while passing through the birth canal. Initial side of colonization is usually gastrointestinal tract. Although as many as 25% of pregnant women experience vaginal candidiasis in late gestation, congenital candidiasis is rare. (Sims 2008) . Although maternal candidemia has been described, hematogenous spread to the fetus has not. Candida spp are also found in the hospital environment in the air, on food, floors and other surfaces and objects, and on the hands of hospital personnel . Colonization of health workers is as high as 30%.

RISK FACTORS

Numerous risk factors for invasive candidiasis have been identified in NICU patients. Some are related to host factors, others, to medical care. Host factors that related to IC including: prematurity , especially extremely low birth weight (Wynn 2011) , Candida colonization, immunodeficiency as a result of decreased numbers of neutrophils and T cell , and immature skin structure . While medical care that related to IC including total parenteral nutrition (Montagna 2010, Manzoni 2014), central venous catheter, mechanical ventilation, use of broad spectrum and/or multiple (Montagna 2010, Benyamin 2010, Avuila-Aguero 2004), use of 3rd generation cephalosporine, administration of H-2 Blockers (Puopolo 2012). Prolonged stay in NICU (Ariff 2011),

colonization with candida and/or prevous episode of mucocutaneus candidiasis, prolonged urinary catheterization , candiduria (Wynn 2011, Montagna 2010).

Preterm infants are predisposed to Candida infection because of immaturity of their immune system and invasive intervention. (Avuila-Aguero 2004)

PATHOMECHANISM AND CLINICAL MANIFESTATION

Although ICI is the most common cause of late onset sepsis, the clinical manifestation may occur earlier at the time of delivery or over the first few days of life as congenital candidiasis. This form is rare in which intrauterine infection is evident at birth. (Sims 2008). In congenital candidiasis cases, the placenta of infants shows evidence of candida infection. These placental findings should prompt close neonatal evaluation. (Pollin). Two form of congenital candidiasis has 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. (Darmstadt, G.L 2000.)

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.

The route of Candida invasion can be endogenous or exogenous. The most important is the endogenous route which the infection is originate from the patient's own colonizing organisms from the gastrointestinal tract and skin (Sims 2008). Infection occurs if there is any defect in the normal host immunity, i.e.: immaturity of cutaneous barrier in neonates that allowing translocation, or disruption of the skin by venous catheter, surgical wound, and trauma. There are two main mechanisms responsible for candidemia. The first is translocation of colonizing Candida across the gut epithelium. (Kaufman 2004). The second mechanism related to the presence of intravenous catheters (Montagna 2010). Infection could be initiated by contamination of the catheter hub at the skin resulting in catheter infection or by transient candidemia from another source resulting in secondary catheter colonization /infection. Whether primary or secondary infection, venous catheters are the prominent final site of Candida infection and can lead to longer candidemia, thrombophlebitis with seeding of organisms into the clot, anfd increased risk of disseminated disease (Sims 2008)

Exogenous route of infection are infrequent but can be important depending on the site of contamination. Multiple related disease have been described, including

candidemia resulting from contaminated blood pressure transducers, contaminated parenteral nutrition solution, and fluids (Sims 2008) and from health workers' hands (Puopolo 2012)

The classic clinical picture of ICI is indistinguishable from bacterial sepsis. Common presenting symptoms are respiratory distress, apnea, thrombocytopenia and localized signs of infection at one or more sites (Sims 2008, Ariff 2011, Puopolo 2012):

Mucocutaneous Candidiasis

Colonization of Candida occurs in 27% of neonate within the first week of life and approximately 8% will develop mucocutaneous candidiasis. Oropharyngeal infection (oral trush) axillary, intertriginous, perineal, and periumbilical are the most common presentations. These diseases are usually self-limited and do not require therapy. However, the rate of IC is significantly higher in neonates <1000 g and do not decrease with topical treatment (Puopolo 2012, Sims 2008)).

Invasive fungal dermatitis is one of severe form of mucocutaneous disease. C. albicans is the most common etiology, but other Candida species, as well as other fungi, can cause the disease. Manifestation occurs from 6-14 of life with erosive, crusting lesions demonstrating fungal infection beyond the stratum corneum. Risk factors include prematurity, post-natal steroid administration, and hyperglycemia (Sims 2008)

Central nervous system :

Candida infection of the CNS is usually secondary to hematogenous disease and presents as meningitis or brain abscess. Meningitis is present up to 64%of fatal cases, and the survivors have a high incidence of severe sequelae including hydrocephalus, psychomotor and mental retardation, and aquaeductal stenosis. Symptoms of Candida meningitis are similar to bacterial meningitis, include fever, confusion, uchal rigidity, and respiratory distress.

***Eyes (ocular Candidiasis*)**

Ocular presentations may be the first presentation of hematogenous spread or may develop after the diagnosis of candidemia and may lead to permanent blindness if not identified (Makhoul 2001) The most common signs and symptoms are eye redness hazy vitreous, pain, and diminished or blurry vision. Premature infants may be at higher risk for developing complicated ocular candidiasis if candidemia occurs around 29

weeks post conception as the lens structures lose their developmental arterial supply and become avascular and less likely to respond to systemic treatment (Sims 2008)). Funduscopic examination is essential for early diagnosis of invasive disease, as the incidence of candida endophtalmitis is as high as 50%.(guideline). A recent consensus document recommends that all patients with candidemia should have at least one careful retinal examination (Makhoul 2001)

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 pulmonary embolism (Makhoul 2001).

Risk factors include presence of a central venous catheter and prior antibiotic therapy (Montagna 2010) although cases without risk factors are described (Sims 2008)

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 (Kaufman 2004)

Bone and Joints : warmth and swelling of the extremities in combination with radiographic evidence of osteolysis or arthritis**.**

DIAGNOSIS

Diagnosis is made by culturing the organism from a sterile site of the body. The gold standard is a positive culture from normally sterile body site such as the blood, cerebrospinal fluid, joint aspirate, sterilely drained abscess, or other sterile surgical specimen. Culture from tracheal aspirates, bronchoalveolar lavage fluid, exposed wound, abdominal drains, epithelium, or other mucocutaneus sources are not diagnostic and cannot differentiate colonization from infection. (Sims 2008, Paupulo 2012)

TREATMENT

Management of Candida infections in the NICU varies widely because there are no FDA-approved antifungal therapies for infants <6 months of age with invasive candidiasis (Ascher 2012). Candidiasis may be treated empirically based on clinical suspicion and risk factors. Current management guidelines for neonatal candidiasis

recommend removing any source of infection such as central venous catheter, unless blood stream infection clears rapidly with antifungal therapy.

Amphotericin B

Amphotericin B is the most commonly used for neonatal antifungal therapy (Prasad 2008), 0.5 to 1 mg/kg/day for duration of 7-14 days after a documented negative blood culture and for longer period if specific end organ infection is present. Thiemedication is given slowly (over 4-6 hours) to minimize the risk of seizures and arrhythmias during the infusion. (CLOHERTY). The drug 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

This drug 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. Doses of 5 mg/kg/day, given over 2 hourswith less irritation at the site of infusion. (Puopolo 2012). Ascher et al reported that infants treated with amphotericin B lipid products had higher mortality than infants treated with either amphotericin B deoxycholate or fluconazole (Ascher 2012).

Flucytosine (5-FC)

The drug interfere 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. Dosis of 50-150 mg/kg/ day (Puopolo 2012). Enteral administration limiting its utility in sick VLBW infants. (Puopolo 2012)

Fluconazole

A fungistatic drug, is the most effective of the azoles (Puopolo). Fluconazole is a potent inhibitor of the fungal cytochrome p450 and sterol C-14 alfa demethylation (Kaufman 2004). Dosis of 6 mg/kg/day. The main side effect is hepatotoxicity, but it is transient and resolves with cessation of therapy. It has decreased activity against C. glabrata and C. krusei (Puopolo 2012)

PREVENTION

Infection control

Candida colonization on the hands and fingernails of health care workers, transmission from patient to patient via health care workers' hands have all been documented. Hand hygiene, either by washing with soap and water or alcohol gels, can reduce health care worker carriage and transmission to patients. Since outbreaks have been linked to the use of artificial nails, wearing of artificial nails should be restricted in the NICU.(Parry 2001). Transmission of Candida to patients has also been described via infusion of intravenous fluids and total parenteral nutrition solutions and via intravascular device and surgical instruments. Handling the instrument properly and proper techniques in sterilizing and preparing the instruments and fluids can reduce hospitalized acquired infection. Minimizing use of broad-spectrum antibiotics (particulaerly cephalosporins) and H2-blockers may be helpful in preventing disseminated candidiasis. The CDC recommends changing infusions of lipid suspensions every 12 hours to minimize microbial contamination; solutions of parenteral nutrition and lipid mixtures should be change every 24 hours (Puopol 2012)

Antifungal prophylaxis

Intravenous fluconazole (6 mg/kg/day) starting during the first 5 days of life and continuing for 4-6 weeks has been shown to reduce Candida colonization and the rate of invasive candidiasis in neonates <1000 g (Kaufman 2001, Healy 2005) and < 1500 g (Bertini 2005). No increased in development of resistant strains of Candida was noted and no adverse events or toxicity was reported. (Puopolo 2012)

One large cohort study in NICU setting reported a decrease in the incidence of ICI during 1997 to 2010 of the study period. During this same time period, they also observed an increased use of antifungal prophylaxis and empirical antifungal therapy as well as decreased use of broad-spectrum antibiotics. These changes in clinical practice may have contributed to the decreased incidence of ICI. (Aliaga 2012)

CONCLUSION

Invasive candida Infection is associated with a high mortality rate. Reporting of systemic fungal infection as well as the spectrum of species involved are essential measure in any intensive care unit in order to implement appropriate preventive and therapeutic strategies.

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