Maternal and Child Health: a Global Perspective

Indonesian - German Health Education Partnership (IGHEP)

MATERNAL AND CHILD HEALTH: A GLOBAL PERSPECTIVE

Editors

Uwe Gross
- Institute for Medical Microbiology, Gerog-August University Goettingen, Germany

Yadi
- Department of Microbiology Faculty of Medicine Mulawarman University, Indonesia

Ni Nyoman Ayu Dewi
- Department of Biochemistry Faculty of Medicine Udayana University, Indonesia

Number of pages: 197 + iv
ISBN: 978-602-294-133-0

Published by: Udayana University Press
Address: Jl. PB. Sudirman Denpasar 80232 Bali

LIST OF AUTHORS

A.A. Raka Budayasa
Department of Obstetrics and Gynecology,
Sanjiwani Hospital, Gianyar-Bali
Email: rakabudayasa@ymail.com

Andri Pramesyanti Pramono
Department of Biology. Faculty of Science and Technology, University of Al-Azhar Indonesia, Jakarta.
email: apramesyanti@gmail.com, pramesyanti@yahoo.com

Andrew Joachim Makoi
International Training & Education Center for Health (I-TECH), Department of Global Health, University of Washington, Dar-Es-Salaam, Tanzania
email: amakoi2001@yahoo.com, amakoi@itech-tanzania.org

Bate Betsy Efudem
Paediatric Unit, Regional Hospital,
Buea Cameroon

Citra Dewi
Department of Obstetrics and Gynecology,
Faculty of Medicine, University of Indonesia
email: wang.cide@gmail.com

Dwi Bahagia Febriani
Department of Child Health, Medical Faculty,
Hasanuddin University

Edward Nketiah-Amponsah
Department of Economics
University of Ghana, Legon, Accra
email: enamponsah@ug.edu.gh, enamponsah@daad-alumni.de

Eric Bertrand Fokam
Department of Zoology and Animal Physiology,
University of Buea, Cameroon,
email: efokam@yahoo.com

Hasanuddin
Department of Obstetrics and Gynecology, Medical Faculty of Syiah Kuala University, Banda Aceh, Indonesia.
email: hasan.spog@yahoo.co.id

Henry Dilonga Meriki
Tuberculosis Section, Laboratory Unit, Regional Hospital, Buea Cameroon

Lily Pertiwi Kalalo
Department of Clinical Pathology, Faculty of Medicine, Mulawarman University Samarinda East Kalimantan
email: lilypertiwi@ymail.com

Matthias Grade
Christliches Krankenhaus Quakenbrück GmbH
Department for Gastroenterology, General Internal Medicine and Infectious diseases, Teaching Hospital of the Medical School of Hannover (MHH), Quakenbrück
m.grade@ckq-gmbh.de

Nelly Al Audhah
Medical Fakulty of Lambung Mangkurat University,
South Kalimantan, Indonesia
email: audhah_fkunlam@yahoo.co.id

Ni Nyoman Ayu Dewi
Department of Biochemistry, Faculty of Medicine,
Udayana University, Denpasar-Bali.
email: ayu.dewi@unud.ac.id

Rahmat Bakhtiar
Departement of Public Health Faculty of Medicine
Mulawarman University Samarinda East Kalimantan
email: bakhtiar_rahmat@yahoo.com.sg

TABLE OF CONTENTS

INVASIVE FUNGAL INFECTION IN NEONATE

Dwi Bahagia Febriani
Department of Child Health, Medical Faculty, Hasanuddin University

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 causes 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 aswell as anti-fungal prophylaxiscan 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).

The route of Candida invasion can be endogenous or exogenous. The most important is the endogenous route which the infection originates 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 hematogenousspread or may develop after the diagnosis of candidemiaand may lead to permanent blindness if not identified (Makhoul, 2001). The most common signs and symptoms are eye rednesshazy 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%. 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 bodysite 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 hours with 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 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, dose 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, 2012). Fluconazole is a potent inhibitor of the fungal cytochrome p450 and sterol C-14 alfa demethylation (Kaufman, 2004). Dose 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 haveall 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 (particularly 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 (Puopolo, 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 infectionas well as the spectrum of species involved are essential measure in any intensive care unit in order to implement appropriate preventive and therapeutic strategies.

REFERENCES

1. Aliaga S, Clark R.H.,Laughon M, Walsh, T.J., Hope W.W., Benyamin D.K., Kaufman D, Arnieta A, Benyamin D.K. Jr, Smith P.B. Changes in the incidence of candidiasis in Neonatal Intensive Care Units. *Pediatrics* 2014;133:236-242.
2. Ariff S, Saleem A.F, Soofi A.B, Sajjad R.Clinical spectrum and outcomes of neonatal candidiasis in a tertiary care hospital in Karachi, Pakistan. J Infect Dev Caries 2011; 5(3):216-223.
3. Ascher S.B., Smith B.P., Watt K, Benyamin D.K., Cohen-Wolkowiez M, Clark R.H., Benyamin D.K., Moran C. Antifungal therapy and outcomes in infants with invasive Candida infection. Pediatric Infect Dis J. 2012 may; 31(5): 439-443.
4. Asticcioli S, Nucleo E, Perotti G, Matti C, Sacco L, Pagani L. *Candida albicans* in a neonatal intensive care unit: antifungal susceptibility and genotypic analysis. NEW MICROBIOLOGICA2007;30:303-307.
5. Avila-aguero M.L., Canas-Coto A, Ulloa-Gutirrez R., Caro M.A., Alfaro B, Paris M.M. Risk factors for Candida infections in a neonatal intensive care unit in Costa Rica. International Journal of Infectious Diseases 2005;9:90-95.
6. Benjamin D.K Jr, Stoll BJ,Fanaroff AA, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18-22 months. Pediatrics 2006;118:717-722.
7. Benjamin D.K Jr, Stoll BJ, GantzM.G, Walsh M.C, Sánchez PJ, Das A, ShankaranS, Higgins RD,Auten,K.J, Miller,N.A, Walsh,T.J.Abbot R. Laptook, MD,jWaldemar A. Carlo,KathleenA. Kennedy, MD, MPH,l Neil N. Finer, MD,mShahnazDuara. Pediatrics 2010;126:e865–e873
8. Chapman RL. Prevention and treatment of Candida infections in neonates.SeminPerinatol 2007;31:39-46.
9. Darmstadt, G.L., j.G. Dinulos, and Z. Miller.2000.Congenital cutaneous candidiasis: clinical presentation, pathogenesis, and management guidelines. Pediatrics 105:438-444

10. Hsieh E, Smith P.B., Benyamin D.K.Jr., Neonatal fungal infection : when to treat? Early hum Dev 2012 may;88 (Suppl 2):S6-S10.
11. Kaufman D, Fairchild K.D. Clinical microbiology of bacterial and funfal sepsis in Very-low-birth-weight infants. CLINICAL MICROBIOLOGY REVIEWS 2004; 638-680
12. Levy I, Shalit I, Askenazi S, et al. Duration and outcome of persistent candidemia in newborn infant. Mycoses2006;49:197-201
13. Makhoul I.R, Kassis I, Smolkin T, Tamir A, Sujov P. Review of 49 neonates with acquired fungal sepsis: further characterization. Pediatrics 2001;107:61.
14. Manzoni P, castagnola E, Jacqz-Aigrain E, Mostert M, Stronati M, Farina D.Invasive candida infections in the nursery: state of the art. SIGNA VITAE 2014;9(2):5-8.
15. Montagna M.T., Lovero G, De Giglio O, Iatta R, Caggiano G, Montagna O, Laforgia N, Aurora project group. Invasive fungal infection in neonatal intensive care units of Southern It;51:125-150.
16. Prasad PA, Coffin SE, Leckerman KH, walsh TJ, Zaotis TE. Pediatric antifungal utilization: newdrugs, new trends. Pediatr infect Dis J. 2008; 27:1083-1088 .
17. Puopolo KM. Bacterian and fungal infection. In: Cloherty JP, Eichenwald, Hansen AR, Stark AR, Eds. Manual of Neonatal Care. Philadelphia: Lippincot:2012:648-650.
18. Roilides E, Farmaki E, Evdoridou J, Franncesconi A, Kasai M, Filioti J, Tsivitanidou M, Sofianou D, Kremenepoulos G , Walsh T.J. Candida tropicalis in a neonatal intensive care unit: epidemiologic and molecular analysis of an outbreak of infection with an uncommon neonatal pathogen. J ClinMicrobiol 2003;41:735-741.
19. Sims C.R, Ootrosky-Zeichner L. Neonatal fungal infection. In: OhlsR.K.,Yoder M.C., Polin R.A., Editors. Hematology, Immunology and Infectious Disease.Neonatology Questions and controversies.Phladelphia: Saunders;2008. 262-278.
20. Steeinbach W.J. Epidemiology of invasive fungal infections in neonates and hildren. Clinical Microbiology and Infection, 2010(16): 321-1327.
21. Wynn L.L., Tan Sylvia, Gantz M.G., das A, Goldberg R.N., Adams-Chapman I, Stoll B.J., Shankaran S, Walsh M.C., Auten K.J., Miller N.A., Sanchez P.J., Higgins R.D.,CottonC.M.,Smith P.B., BenyaaminD.K.Jr., the NICHD Neonatal Research Network. Outcomes following candiduria in extremely low birth weight infants. CID 2012;54: 334-339.