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CASE SERIES

AN OUTBREAK OF CANDIDEMIA AMONG HOSPITALIZED NEONATES AT TIKUR ANBESSA SPECIALIZED TEACHING HOSPITAL: A CALL FOR INCREASED AWARENESS

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ABSTRACT

Introduction*: Candida species are a prominent cause of hospital-onset blood-stream infections. Newborns and infants are notable risk groups. The clinical course of 17 neonates who developed hospital acquired Candidemia at Tikur Anbessa Specialized Teaching Hospital, Addis Ababa, Ethiopia is described in this article. Because of diagnostic limitations hitherto, fungemias hadn't been given due attention in the hospital.*

Objectives: *The objective for this case series is to describe the presentation, diagnosis and management of newborns diagnosed with candidemia at the Tikur Anbessa Specialized Hospital, Addis Ababa.*

Methods: *A case series documented by charting the presentation and management of neonates diagnosed with Hospital-onset Candidemia from January – August 2018 is described. Extracted data was summarized using descriptive statistics (frequencies).*

Results: *Eleven female and six male newborns were diagnosed with Hospital-onset Candidemia. Thrombocytopenia featured prominently in their lab work-up. The patients took a mean of thirteen days of parenteral antibiotics before diagnosis, which was confirmed by blood cultures. Seven had C. albicans and ten had non-albicans Candidemia.*

Conclusion*: The illness and treatment course of 17 newborns treated for Candidemia at the Tikur Anbessa Specialized Teaching Hospital, Addis Ababa, Ethiopia, are charted. Awareness on risk factors and prevention is of utmost importance to limit the high mortality associated with Invasive candidemia.*

Key words: *Candidemia, Ethiopia, Newborns, Infants, albicans, non-albicans*

INTRODUCTION

Candida species are the fourth most common cause of blood-stream infections (BSIs) in intensive care. They are also among the top ten causes of community onset BSIs (1). Predisposing factors include prolonged hospitalization, use of broad-spectrum antibiotics, newborns (particularly pre-terms and those with low birth weight), abdominal surgery, immune-compromise, critical illness, hemodialysis and acute necrotizing pancreatitis (2).

The incidence of Candidal BSIs in sub-Saharan Africa has been rising over the past decade. An analysis of BSIs at a tertiary Kenyan hospital revealed that *Candida* were the most common causes (34%) of hospital-onset BSIs with three fourth of isolates being non-*albicans* species (3). A prospective cohort of Tanzanian children aged 7 years or less showed that Candidemia accounted for 9% of all BSIs (4).

Candida species (especially *C albicans* and *C parapsilosis*) are the third most common isolates from South African neonatal intensive care units with an attributable mortality of 46% (5,6).

While the proportion of Candidal BSIs due to *C albicans* in Africa is declining, the more difficult to treat non-*albicans* species (*C glabrata*, *C parapsilosis*, *C krusei* and *C auris)* are on the rise. This has been especially observed from hospitalized children in South Africa (8 – 9). Ben Abdeljelil et al also observed a shift towards non-*albicans* species (esp. *C parapsilosis)* among neonatal invasive candidiasis in a Tunisian hospital over the period between 1995 and 2010 (10).

Blood cultures can be used to diagnose Candidemia, albeit with a lower sensitivity and a slow turn-around time. Germ tube testing is used to confirm *C albicans* infection. It was first reported by Reynolds and Braude in 1956 and Taschdjian in 1960. *)*.

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Germ tubes are features of *C albicans* which are short, non-septate hyphae (differentiates it from most species) without constrictions at their point of origin (differentiates it from *C tropicalis)*. Their formation is associated with increased synthesis of protein and ribonucleic acid. A heavy inoculum will inhibit germ tube formation (11). *Candida* mannan antigens and antibodies have a good negative predictive value with rapid results in areas with low prevalence. More conclusive test include Polymerase chain reaction (PCR) analysis (11,12).

Candidemia in neonates is treated by Amphotericin B with Fluconazole being an alternative for newborns who haven't been exposed to it. Echinocandins serve to treat those with resistant *Candida* isolates (*C. krusei*, *C. glabrata* etc) or when newborns develop Fluconazole or Amphotericin B related toxicity. Treatment is continued for 2 weeks following negative blood cultures and symptoms' resolution in newborns without metastatic complications (13).

Though a multitude of studies have been conducted in Ethiopia concerning mucosal Candidiasis and Candiduria, there is a paucity of clinical data on invasive Candidemia – both in children and adults (7). The objective for this case series is to describe the presentation, diagnosis and management of newborns diagnosed with candidemia at the Tikur Anbessa Specialized Hospital, Addis Ababa.

PATIENTS AND METHODS

Study area

Tikur Anbessa specialized hospital is the largest tertiary referral hospital in Ethiopia. It has 800 beds and gives specialty care via a diverse array of disciplines. The neonatal intensive care unit (NICU) has 40 beds and includes preterm neonatal care, neonatal surgical

Study design

A case series documented by charting the presentation and management of neonates diagnosed with Hospital-onset candidemia from January – August 2018 is described.

Study population

All identified cases of Candidemia among neonatal ICU admissions within the eight months of January – August 2018 are analyzed.

Data collection, quality and analyses

Demographic, clinical and microbiological data were extracted from charts of affected newborns. A descriptive quantitative analysis of collected data was then made.

Ethical considerations

Photos of patients and any other identifiers were not used when analyzing clinical and microbiological data.

RESULTS

Overall, eleven female and six male neonates were diagnosed with Candidemia over an eight month period (January – August 2018); ten of which were diagnosed in the two months of July and August 2018 (Figure 1). The mean age at diagnosis was 11.8 days. All neonates were preterm deliveries with a mean gestational age of 31 weeks and 6 days and mean birth weight of 1488 grams.

Co-morbidities at the time of admission for the series of neonates were in keeping with their prematurity – Respiratory distress syndrome, Necrotizing enterocolitis and Patent ductus arteriosus. At the time of their Invasive candidemia diagnoses, the newborns had received an average thirteen days of a mean of three antibiotics. None exhibited oral candidiasis.

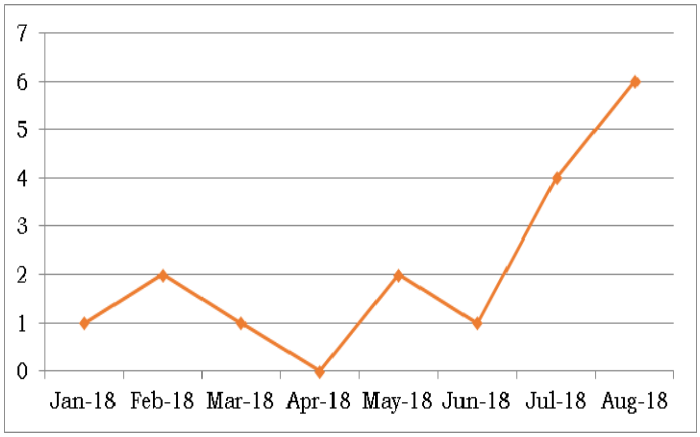

Figure 1: Diagnoses of invasive Candidemia in the neonatal intensive care unit of Tikur Anbessa Specialized hospital (January – August 2018)

Affected newborns presented with persisting fever or hypothermia, poor feeding and depressed neonatal reflexes despite respiratory support and prolonged parenteral antibiotics. The clinical diagnosis of a fungemia was based upon the fulfillment of all of the following criteria in these newborns:

- A lack of response to multiple courses of empiric antibiotic treatments
- Presence of at least one clinical risk factors for fungemia (preterm delivery, prolonged peripheral cannulization, abdominal surgery)
- Presence of laboratory predictors of fungemia like persisting unexplained anemia, leukopenia or thrombocytopenia

Quantitative serum C-reactive protein was measured in 14 of the 17 newborns and it was elevated in only a third of tests. Two-thirds (twelve) exhibited persistent thrombocytopenia (mean platelet count: 38,300/mm^3) despite negative serologic tests for other infectious etiologies like congenital toxoplasmosis, cytomegalovirus and syphilis and negative blood cultures for aerobic bacteria. Eight newborns had unexplained anemia (mean hemoglobin: 10.8 gm/dl) in serial determinations and three had persisting leukopenia (mean white blood cell count: 2,955/mm^3) for which an etiology could not be identified.

Following the fulfillment of the above clinical criteria, blood cultures were drawn with a request to observe for yeast cells after a minimum of five and a maximum of seven days of incubation.

Cure from candidemia was taken as negative blood cultures after uninterrupted antifungal treatment (in the absence of administration of antibiotics or antivirals) and clinical resolution of presenting illness.

Microbiologic procedures

Following the collection of blood culture specimens and observation of creamy white, glistening colonies on plates, gram staining was done Figure 2. A germ tube test was then performed to differentiate between *albicans* and non-*albicans* candida. With a light suspension of suspect yeast colonies made on serum in tube, the suspension was incubated at 35^0C – 37^0C for 3 to 4 hours. After a drop of suspension was placed on a slide, a wet mount was examined production of germ tubes (projections extending from yeast cells).

The presence of short, slender non-septated tubes without constriction at their point of origin confirmed a likely diagnosis of *Candida albicans* (Figures 3 and 4) and their absence was interpreted as non-*albicans Candida* blood stream infection (BSI). Further confirmatory tests on samples (e.g. *Candida* mannan antigens, PCR tests) could not be performed in the hospital's microbiology laboratories.

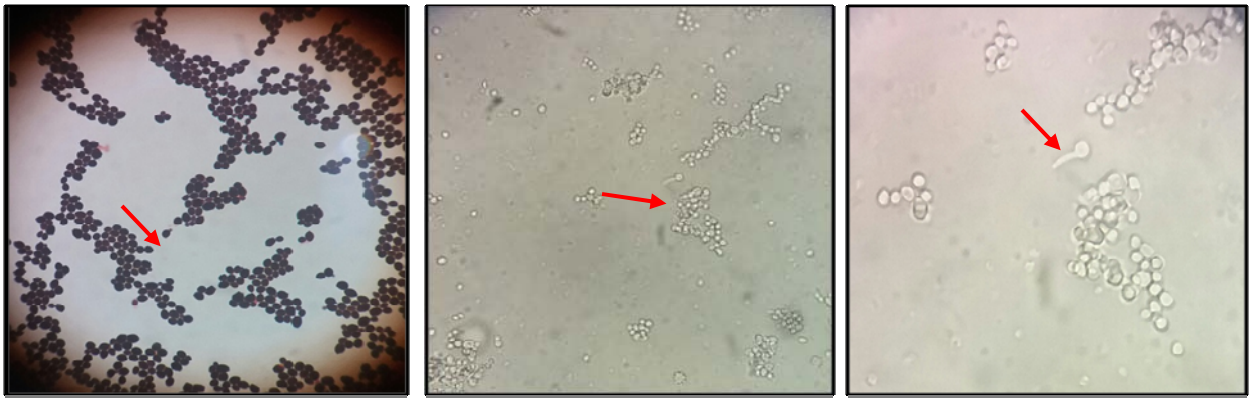

Figure 2: Gram positive budding yeasts **Figures 3 & 4** (arrows): Yeast cells with non-septate hyphae Microbiologic isolates from three newborns.

Of the isolates, ten were non-*Candida albicans* while seven were *albicans*. Anti-fungal susceptibility testing could not be done at our hospital. Based on standard recommendations for treating neonatal Candidemia (13) while monitoring availability of different anti-fungals within the hospital's pharmacy as well as privately owned medicine retail outlets, an empiric treatment with Fluconazole was planned. A shift to intravenous Caspofungin or Amphotericin B when faced with a lack of improvement in neonates with non-*albicans* species was also offered.

Four newborns improved on their illness (One with *C. albicans* sepsis and three with *C.* non-*albicans* sepsis) after being treated with a two-week course of intravenous or oral Fluconazole (while simultaneously discontinuing antibiotics) and were discharged. Two patients succumbed to their illness after starting treatment (one with a *C. albicans* isolate after three days of Fluconazole and another with a non-*albicans* isolate after being treated with three days of Fluconazole followed by eight days of Caspofungin). The rest eleven died due to an untreated Candidemia because of a lack of availability of anti-fungals in the hospitals' formulary or due to caretakers' being unable to cover the expensive costs of antifungals on sale at privately owned medicine retail outlets.

DISCUSSION

The NICU of the Tikur Anbessa specialized teaching hospital admits more than 2800 neonates per annum – averaging close to 235 per month. All confirmed candidemias from the NICU were from preterm neonates. Only four neonates survived their illness while the rest died due to a delayed diagnosis, a virulent strain or more often than not, a lack of affordable options of anti-fungal drugs. Ten newborns had sepsis due to non-*albicans Candida*. One had complicated with thrombophlebitis. The occurrence of these nosocomial neonatal infections qualifies as an outbreak in the study hospital as an increased incidence from preceding times (when diagnosis was either not considered or a limitation existed in confirming clinical diagnoses) was documented.

We utilized a low-cost technique to diagnose Candidemia in these patients but were limited by lack of further confirmatory testing. The growing incidence of Candidemia can be curbed by frequent changes in intravenous lines, targeted investigations for at-risk preterms including those undergoing gastrointestinal surgeries and limiting use of broad-spectrum antibiotics while adhering to recommended durations of antimicrobial therapy and discontinuing at the earliest opportunity.

The incidence, speciation and resistance profile of hospital-acquired candidemia at the Tikur Anbessa Specialized teaching hospital should be further analyzed. The need for such a study is particularly important in light of its contribution in preventing the unjustified use of parenteral antibiotics in early life sepsis without a confirmed bacterial etiology leading to multi-drug resistant hospital pathogens.

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Competing interest

The authors declare that this manuscript was approved by all authors in its form and that no competing interest exists.

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