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Humanitarian And Resource-Limited Setting

Retrospective analysis of fungemia among children in Anka General Hospital, Nigeria, from October 2018 to November 2021: a case series

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Abstract

Yeast-related bloodstream infections (BSIs) in pediatric patients are associated with severe acute malnutrition (SAM), hematological/oncological malignancies and admission to an intensive care unit. These infections are rarely described from low- and middle-income countries. We describe a case series of pediatric patients diagnosed with severe sepsis and yeast isolated from their blood culture in a conflict-affected area of Nigeria from October 2018 to November 2021. We identified 20 patients with yeast BSIs, among whom 17 were also diagnosed with SAM. We recommend the inclusion of antifungal treatment for empiric treatment guidelines for children with SAM and severe sepsis in similar settings.

INTRODUCTION

Candida is the most common cause of invasive fungal infection in humans, which may progress to candidemia (presence of *Candida* in the blood). Globally, there has been an upward trend in recent years of candidemia; thus, timely diagnosis is crucial for appropriate clinical management and prevention of mortality [1]. These infections contribute to substantial in-hospital morbidity and mortality and are associated with an increased financial burden [2]. Bloodstream infections (BSIs) with yeast present with non-specific clinical signs and symptoms, making them difficult to distinguish from other infectious causes. Diagnosis of candidemia requires the detection of Candida in blood cultures, but this technique has low sensitivity and cultures may require several days to become positive [3].

In children, the risk factors for candidemia are different from adults [4] and include severe acute malnutrition (SAM; weight-for-height *Z* score <-3 or bilateral edema and/or mid-upper-arm-circumference <125 mm) [2], underlying hematological/oncological malignancies [5], admission to a neonatal or pediatric intensive care unit [1], presence of a central venous catheter and severe immunosuppression (i.e. human immunodeficiency virus/acquired immune deficiency syndrome) [6].

All-cause mortality associated with pediatric candidiasis exceeds 15%, with an attributable mortality of 10% [7]. However, detailed knowledge of the epidemiology of Candida species among children is limited, particularly in sub-Saharan Africa [4]. To our knowledge, only one large international pediatric multi-institutional study on *Candida* sp. infections in children has been conducted in Europe [4].

Médecins Sans Frontières (MSF) and the Ministry of Health (MOH) collaborate in Anka General Hospital (AGH), Zamfara State (Nigeria). Since October 2018, MSF and the MOH have implemented microbiological surveillance for suspected cases of community-acquired sepsis and treatment failure in admitted children as a part of antibiotic stewardship activities. Yeast has been isolated from a number of blood cultures during these surveillance activities [5]. The current MSF pediatric guidelines include recommendations for antifungal treatment

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for children with oral thrush only, and there are no treatment recommendations for yeast BSIs in the Nigerian MoH guidelines [6, 8]. As serious fungal infections in children have not been extensively described in Nigeria [9], we aimed to improve our knowledge of yeast as a cause of BSIs of pediatric patients with the clinical diagnosis of severe sepsis.

METHODS

Setting

AGH is a secondary health care structure located in a conflict-affected area in Anka, Zamfara State, northwest Nigeria. The hospital emergency triage functions as the sole point for hospital admission to the isolation, the in-patient and the in-patient therapeutic feeding Centre (ITFC) wards (150 beds total).

Study design and population

A retrospective case-series study of the clinical and microbiological features of pediatric in-patients with severe sepsis (<5 years) on admission, or with treatment failure during hospitalization (see Box 1 for case definition), who had a yeast identified in their blood cultures between October 2018 and November 2021.

Box 1. Case definition for pediatric severe sepsis at admission and treatment failure during hospitalization in AGH protocol [10]

The current case definition for pediatric severe sepsis in AGH is:
All pediatric patients who are >2 months of age, who present to Anka pediatric triage, and have:
At least 2 (TWO) of the criteria below:

- Axillary temperature >38 °C or <35.5 °C;
- Tachycardia or Bradycardia for age
- Tachypnea for age and/or Oxygen Saturation <92%;
- Leucocytosis or leukopenia or >10% immature neutrophils.

PLUS
At least 1 (ONE) of the criteria below:

- Decreased level of consciousness (AVPU: P + U);
- circulatory insufficiency: tachycardia + at least one of: weak pulse *or* capillary refill time >3 seconds *or* oligo-anuria.

The current case definition for treatment failure in AGH is:
Any patient in the hospital being treated for an infection + at least 48 hours of clinically appropriate antibiotics and no improvement or worsening of at **least two of the vital signs**; these can include:

- Axillary temperature >38°C or <35.5 °C;
- Tachycardia or bradycardia for age;
- Tachypnea for age and/or oxygen saturation <92%
- Decreased level of consciousness (AVPU: P + U)
- Circulatory insufficiency: tachycardia + at least one of: weak pulse *or* capillary refill time >3 seconds *or* hypotension *or* oligo-anuria.

IN ADDITION: No obvious source control problem (e.g. an intra-abdominal abscess that needed drainage).

Microbiological procedure

Blood culture samples were collected from patients meeting eligibility criteria for severe sepsis and treatment failure using an aseptic technique. A blood volume of 1–2 ml was collected from pediatric patients <1 year of age, and for pediatric patients ≥1 year of age, a blood volume of 2.5–5 ml was collected. These samples were directly inoculated into aerobic culture medium bottles (Liofilchem-490030 and Liofilchem-490050, respectively); the samples were transported immediately after collection to the laboratory. Samples were incubated at 35°C and were analyzed according to standard operating procedures (SOPs) for blood culture in the laboratory. The isolation of yeast follows the same SOP; identification is done using growth on solid chocolate media by macroscopic observation of the colonies and by direct microscopy of the gram stain. Pure culture was obtained using chromogenic agar from positive yeast isolate and was followed by Gram stain. The result of the yeast was discussed with the antibiotic stewardship focal point in AGH to clarify if the isolated yeast was considered to be pathogenic or as a contaminant. Late in the study period, we added germ-tube testing for presumptive identification of *Candida albicans*. Other tests to identify other species of fungi (i.e. biochemical, molecular or immunological) or tests to identify resistance to antimycotics were not available in the laboratory.

Data collection

Demographic and clinical characteristics data were extracted from routine health information databases. Microbiological data and patients' information were extracted from the WHONET microbiological database (www.whonet.org) by R.O. and F.C. All data collected were encoded into a specifically designed database in Epi Info version 7.2 by RO; the encoded data were verified by E.R., K.C. and A.L.

Data analysis

We calculated descriptive statistics for all clinical and microbiological characteristics using Microsoft excel. F.C., E.R. and K.C. judged the appropriateness of antimicrobial treatment before and after blood culture results based on the drug choice, dose, frequency, route and antimicrobial association according to the MSF treatment protocol [7, 11].

RESULTS

Among 656 patients with clinically diagnosed severe sepsis and/or treatment failure for whom a blood culture was taken during the study period, 24 patients (3.7%) had yeast isolated. Of these, four patients (16.7%) were excluded because of incomplete data. Of the 20 patients included in this study, 12 (60%) were female, 11 (55%) were aged between 6 and 23 months and 13 (65%) were admitted to the ITFC ward (Table 1, Appendix 1). Seventeen patients (85%) were categorized as SAM. Nine (45%) patients developed severe sepsis as a result of treatment failure (i.e. after admission to the hospital; Table 1). All the patients in the study had a peripheral venous catheter with an average dwell time of 7 days. The patients under review received antibiotics before the onset of fungemia, and they were all prescribed with ceftriaxone following the MSF treatment guidelines. Seven patients (35%) had appropriate antibiotics administered

Table 1. Demographic and clinical characteristics of patients with yeast isolated in their blood culture, Anka Nigeria, 2018–November 2021

Patient distribution	Total (N = 20)	
Characteristic	**n**	**%**
Sex		
Female	12	60
Male	8	40
Missing	0	0
Age group (months)		
6–23	11	55
24–>/=48	7	35
Missing	2	10
Ward admitted to		
ITFC	13	65
Pediatric	5	25
Isolation	1	5
COVID	1	5
Temperature		
>38	12	60
<38, but >35.5	3	15
<35.5	5	25
Severe sepsis		
Community-acquired		
Chest focus	6	30
Gastrointestinal (GI) tract focus	2	10
No focus specified	2	10
Meningitis (central nervous system)	1	5
Treatment failure		
Chest focus	3	15
GI tract focus	2	10
Upper respiratory focus	1	5
Chest focus + malaria	1	5
No focus specified	1	5
GI + malaria	1	5
SAM		
Yes	17	85
No	3	15
HIV Status		
Unknown	5	25
Positive	1	5
Negative	14	70
Clinical outcome		
Cured	5	25
Transfer to MSF ATFC	8	40
LAMA	1	5
Dead	6	30
Category of duration of hospitalization		
1–5 days	8	40
6–11 days	5	25
≥12 days	7	35
Time from admission to death (for those that died; N = 6)		
1–5 days	3	50.0
6–10 days	1	17.0
11–15 days	1	17.0
≥16 days	1	17.0

N, number; ATFC, ambulatory therapeutic feeding center.

before blood culture, while none of the patients had appropriate treatment after blood culture results; of the 20 patients in the case series, 15 (75%) either left against medical advice (LAMA)/were discharged home or died at the time of culture confirmation (Table 1).

DISCUSSION

In AGH, we found that in children with severe sepsis at admission or with treatment failure, 20 (3.7%) had a confirmed yeast BSI. This is lower than the prevalence of candidemia identified among BSIs in children in the USA (11%) and in Egypt (17.3%) [11, 12]. Mortality was high in this case series (30%), but it was similar to that described in a previously conducted study on community acquired BSIs in the same hospital [8]. The majority of the patients were diagnosed with SAM ($n = 17$, 85%), which is a well-described risk factor for yeast-related BSIs [4]. This is an especially relevant finding as acute malnutrition cases in Nigeria are clustered in the northern part of the country [13, 14].

None of the patients in the case series received appropriate antimicrobial treatment after blood culture results were available due to the absence of intravenous antifungals in AGH and the lack of clear treatment guidelines for this infectious condition [7, 8]. The results of this study should therefore urge a revision of current treatment guidelines for severe sepsis, particularly in children with SAM.

We found a high proportion of patients with yeast BSIs ($n = 9$; 45%) who had severe sepsis diagnosed at the time of treatment failure. This may suggest that these specific BSIs were most likely hospital-acquired infections and a potential entry point could be the peripheral venous catheter, as all patients had one and for a median dwell time of 7 days. Pediatric patients with SAM have been shown to be at a higher risk of hospital-acquired bacterial infections in studies from Ethiopia [15] and Kenya [16]. It is likely that the risk for hospital-acquired yeast infections would be similar. This underscores the need for strong infection, prevention and control measures in ITFCs.

Unfortunately, we were unable to conduct identification of yeast at species level for most of the cases due to the absence of germ tube test supplies; only one *C. albicans* was identified at the point when the germ tube test was introduced. These have since been procured for the laboratory to conduct the additional microbiological testing. Also, due to the retrospective nature of the study, it was difficult to analyze the appropriateness of antibiotic prescriptions for these patients. We might have overestimated the yeast BSI mortality in our study population. Considering that SAM is a complex clinical condition, the cause of death in these patients might have been multifactorial and not only related to the yeast infection [17]. This study reveals that the isolation of yeast in blood culture among pediatric patients with a clinical profile of severe sepsis and SAM is not negligible. It is the first case series from Zamfara state in northwest Nigeria showing this result. This study highlights the need to include antifungal treatment in Nigerian hospitals where an increased number of patients with severe sepsis and SAM are being admitted. We encourage others to document more specific findings around the epidemiology, clinical management and risk factors for pediatric patients with yeast BSIs in low-resource settings.

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ETHICAL APPROVAL AND CONSENT

Ethical approval was obtained from the Zamfara state MOH Ethics Department and the National Health Research Ethics Committee of Nigeria (ZSHREC03102021). A general consent procedure for routine data collection was implemented in AGH from August 2021. This research fulfilled the exemption criteria set by the MSF Ethics Review Board for a posteriori analyses of routinely collected clinical data and thus did not require MSF ERB review. It was conducted with permission from Medical Director, Operational Center Amsterdam, MSF.

CONFLICT OF INTEREST STATEMENT

None declared.

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Appendix 1. Case definition for ITFC and ATFC

ADMISSION CRITERIA

- ✓ Edema +++ or
- ✓ Referred from outpatient care to finish treatment
- ✓ Edema + or++ and/or
- ✓ WHZ <−3 and/or
- ✓ WHZ >−3 and <−2 and/or
- ✓ MUAC <125 mm (<12.5 cm)

Plus

- ✓ Medical complications needing in-patient admission and/or
- ✓ Anorexia/failed appetite test