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Invasive Candidiasis in Neonatal Care

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Abstract

Neonatal invasive candidiasis is associated with significant morbidity and mortality. It refers to all infections requiring the use of an invasive antifungal agent and includes: catheter infections, urinary tract infections, meningitis, and any other Candida infection of a normally sterile body fluid. The factors that favor the occurrence of invasive candidiasis are premature birth and the existence of umbilical venous catheter or digestive surgery and exclusive parenteral nutrition. The aim of our study is to determine the epidemiology and risk factors of postnatal invasive candidiasis in the neonatal medicine and intensive care unit of the Abderrahim Harouchi Children's Hospital in Casablanca, Morocco, and to describe the main clinical, biological, therapeutic and evolutionary characteristics of invasive candidiasis.

Introduction

Neonatal invasive candidiasis refers to all infections requiring the use of an invasive antifungal agent and includes: catheter infections, urinary tract infections, meningitis, and any other Candida infection of a normally sterile body fluid [1]. They are rare but serious. There is a direct relationship between the extent of neonatal colonization and the risk of invasive infection [2]. The incidence of invasive candidiasis in newborns remains poorly known in Morocco. Thetransmission at the origin of neonatal colonization is most often vertical, maternal-fetal, antenatal or per partum, sometimes postnatal. This transmission can lead to colonization or congenital candidiasis with cutaneous and/or mucosal involvement in full-term newborns, but also to diffuse and invasive involvement, particularly in premature babies [3]. The factors thatfavor the occurrence of invasive candidiasis are essentially represented by very premature birth and the existence of umbilical venous catheter or digestive surgery and exclusive parenteral nutrition [4]. The aim of our study is to determine the epidemiology and risk factors of postnatal invasive candidiasis in the neonatal medicine and intensive care unit of the Abderrahim Harouchi Children's Hospital in Casablanca, Morocco, and to describe the main clinical, biological, therapeutic and evolutionary characteristics of invasive candidiasis.

Patients and Methods

We conducted a retrospective study over a period of 18 months (January 2020-June 2021) in the Department of Medicine and Neonatal Intensive Care at the Abderrahim Harouchi Children's Hospital in Casablanca. The inclusion criteria were as follows:

- All newborns who have developed a postnatal Candida infection.
- Patients with cutaneous candidiasis and neonates who underwent abdominal surgery were excluded from the study population.
- Epidemiological, clinical, paraclinical, therapeutic and outcome information was obtained from the medical records.

Results

Over an 18-month period, 22 cases of invasive candidiasis were collected. The age of admissionof the newborns varied from one hour to 28 days of life. There was a slight female predominance: 12 girls (54.5%) and 10 boys (45.5%). 68.1% of newborns were premature. Nohistory of cervical cerclage or intrauterine device was noted among the mothers. 54.5% of the newborns were delivered by caesarean section, the median birth weight was 1740 grams [1300-3450 grams]. The reason for admission was dominated by neonatal respiratory distress (86.3%), 1 patient was admitted for sepsis and 2 patients for urinary infection. Concerning the predisposing factors to invasive candidiasis, 14 neonates (63.6%) benefited from umbilical venous catheter (Uvc), 69% of the neonates were on mechanical ventilation, parenteral nutrition was unsaturated in 68.1% of patients. All neonates were on broad-spectrum antibiotic therapy (**Figure 1**). The average length of hospital stay was 30 days [27-53 days]. The mean time to onset of invasive candidiasis in our series was 11 days.

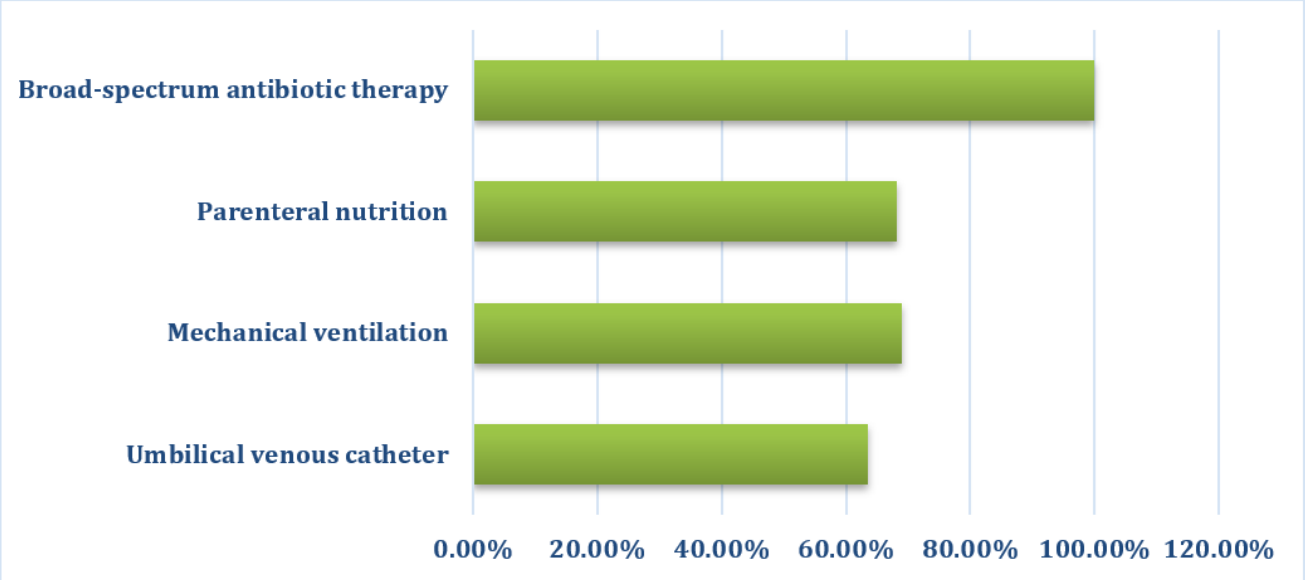

Figure 1: Risk factors for invasive candidiasis.

In our series, the main clinical circumstances of discovery were dominated by apnea (12 cases), hyperglycemia (4 cases) and hypothermia (3 cases). We noted 1 case of meningitis complicated by brain abscess, while 3 newborns were asymptomatic (isolation of Candida on invasive devices: Uvc.

We noted hyperleukocytosis with predominantly neutrophils in 3 neonates (>25000/mm^3), thrombocytosis in 1 case. CRP was negative in 17 newborns (77.2%).

The main sites of isolation were urine in 10 cases (45.4%), blood in 8 cases (36.3%), Ktvo in 3cases (13.6%) and 1 case in the brain pus. The predominance of *Candida Albicans* was evident in our series (95.4%), only 1 case of *Candida Parapsilosis, o*f all the antifungals performed, the sensitivity to Fluconazole was 96% and 4% to Amphotericin B. The average duration of treatment was 21 days. No cases of renal damage (Fungus Ball) were noted.

A brain CT scan was performed in a neonate and showed a left temporoparietal brain abscess with a ventriculitis appearance.
The outcome was favorable and without sequelae in 15 cases (68.1%). 7 newborns died withsepsis. Bacterial co-infection was noted in 7 patients, the main germs isolated at blood culture were: Klebsiella Pneumoniae (3 cases), Enterobacter spp (1 case), Pantoea spp (1 case), Acinetobacter Baumannii (1 case), Raoultella Terrigena (1 case).

Discussion

Invasive candidiasis is an important cause of sepsis in neonatal intensive care. Neonatal Candida infections are classified according to their age of onset into early infections, otherwise known as maternal-fetal infections (MFIs) occurring within the first four days of life, as well as late primary infections and nosocomial infections. [5,6]. Candida is the third most commoninfectious agent responsible for nosocomial catheter infections in the United States [7]. The three-year cumulative incidence rate of invasive candidiasis in a cohort of 2,847 neonates hospitalized in six US neonatal intensive care centers ranged from 2.6% to 16.7% in neonates weighing less than 1500 grams and 20% in neonates weighing less than 1000 grams [8].

In preterm neonates weighing less than 1500 grams, invasive Candida infection is often preceded by colonization, which may occur either horizontally (transmission by nursing staff, equipment) or vertically (passage through the genital tract), the latter being the more frequent mechanism [9]. The incidence of nosocomial Candida infections in neonatal units increased significantly in the early 1990s, from less than 5 per 1000 admissions to more than: 12/1000 for Saiman et al [10].

Invasive candida infection most commonly affects premature infants; this is explained by immune failure leading to disturbances in cytokine production, phagocytosis, and defects in antibody production. Immature skin associated with invasive medical devices leads to invasivefungal infection [1]. In our series, we noted a high prematurity rate of 68.1%, which is in line with the literature.

Low birth weight is a criterion that increases the risk of invasive candidiasis in a newborn; indeed, this infection occurs in 11.4% of newborns weighing 400-750 g at birth compared to only 3.4% in those with a PN between 750 and 1000 g [11,12]. The median birth weight in ourseries was 1740 g.

Candida species are able to burrow into invasive medical devices (venous catheter, intubation probe) and create a biofilm that provides a new defense barrier and prevents the penetration ofantifungal agents, thus protecting the yeasts from host immune responses [13,14]. Our results are in line with the literature, we noted invasive candidiasis in 63.6% of neonates who underwent Uvc and 69% of those who were on mechanical ventilation.

The use of broad-spectrum antibiotics has been described in several series as a risk factor for neonatal invasive candidiasis, particularly third generation cephalosporins which disrupt bacterial balance and release muramic acid which promotes Candida proliferation and pathogenesis [15,16]. All our patients have received broad-spectrum antibiotic therapy for healthcare-associated infection.

The use of parenteral nutrition and a prolonged stay in neonatal intensive care (>7 days) are also incriminated as risk factors for invasive candidiasis [17,18]. 68.1% of our patients were on parenteral nutrition while the average length of stay in our series was 30 days.

During candidiasis, clinical signs in the newborn are non-specific and often subtle. These include temperature instability, lethargy, apnoea, hypotension, respiratory distress, abdominal distension, hyperglycaemia and feeding intolerance. The prolonged period of candidaemia is associated with an increased risk of dissemination, which may occur when the fungal blood culture is not positive [19]. In our series, we noted positive blood cultures in 36.3% of cases.

Candida infection of the urinary tract in neonates may be limited to isolated candiduria or mayinvolve parenchymal involvement with multiple abscesses. It may be either haematogenous or ascending. Neonates with congenital renal or urinary tract disease, anatomical obstructive disease or neurological abnormalities that promote urinary stasis in the bladder are at increasedrisk of developing renal candidiasis, particularly in the form of Fungus ball that can be easily identified on renal ultrasound [8].

Bacterial-fungal co-infection is responsible for a threefold increase in neonatal mortality, withthe main germs being coagulase-negative Staphylococcus, Staphylococcus aureus and Enterococcus spp. This is explained by the invasion of medical devices and biofilm formation [20].

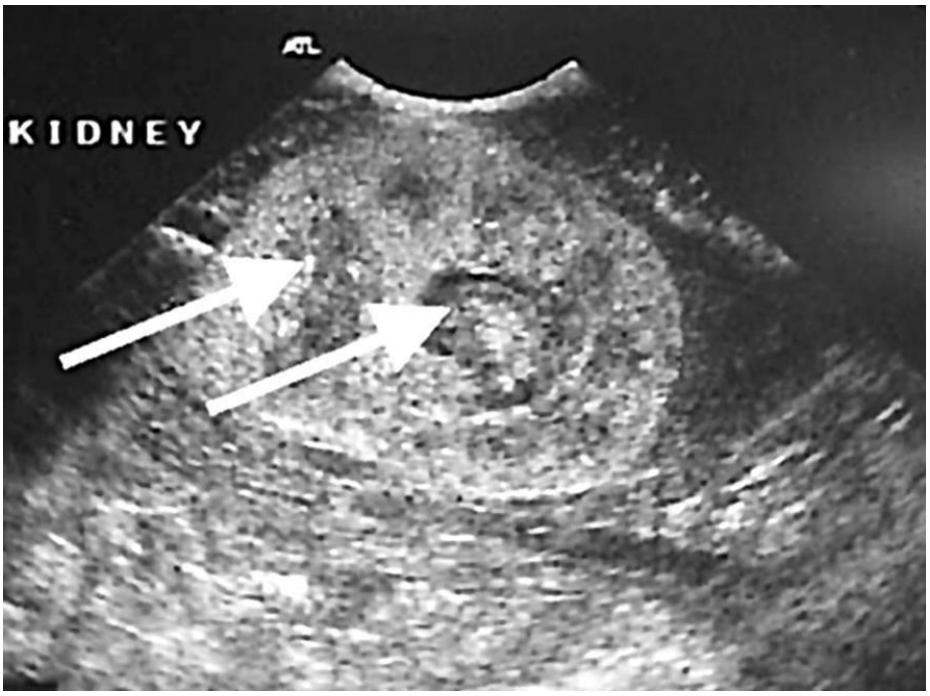

Figure 2: Fungus Ball appearance detected on renal ultrasound [8].

The frequency of central nervous system (CNS) infection in neonates with invasive Candida infection is highly variable in the literature (up to 50% in publications from the 1980s [3,8,21].It seems to have decreased and the most recent studies report a frequency of intrameningeal involvement in preterm infants with a positive Candida blood culture of 10% [22]. The most common clinical form is neonatal meningoencephalitis but brain abscesses, ventriculitis, vasculitis and perivasculitis have been described [22]. More rarely, seizures, focal neurological signs or an increase in head circumference with a tense fontanel may reveal central involvement [3]. CNS involvement should be systematically considered in all newborns with apositive Candida blood culture. We found only one case of meningitis complicated by brain abscess and ventriculitis, and this patient was co-infected with Klebsiella Pneumoniae.

The existence of hyperglycaemia and its persistence, and a thrombocytopenia without obvious explanation, should raise the diagnosis of neonatal invasive candidiasis. Suspecting a fungal infection in the presence of a "hyperleukocytosis - low CRP" association is predictive in neonates who may present neutropenia in this type of infection [3]. The biological abnormalitiesthat we noted in our patients were represented by a hyperleukocytosis with a predominance ofneutrophils in 3 newborns, no case of neutropenia was noted and thrombocytopenia in 1 case, the CRP was negative in 77.2% of newborns.

The biological diagnosis of invasive neonatal candidiasis is based on the isolation of Candida from the various samples taken. All newborns suspected of having a fungal infection should have a urine examination, a lumbar puncture and a blood sample [23].

A dozen species of Candida are pathogenic to the newborn out of nearly 200 species identified.Candida Albicans is the species most often responsible for neonatal Candida infections [8]. These data are similar to our results, we noted a clear predominance of Candida Albicans infections against only 1 case of Candida Parapsilosis.

The therapeutic management of neonatal invasive candidiasis is based on three major families of antifungal agents: amphotericin B and its derivatives, azoles and echinocandins. The use of 5-fluorocytosine is controversial. We quote below the Infectious Diseases Society of America (IDSA) recommendations for the treatment of neonatal invasive candidiasis developed in 2009and updated in 2016 [24]:

- Amphotericin B deoxycholate at a dose of 1 mg/kg/d is recommended for neonates with disseminated candidiasis. In the absence of urinary tract involvement, lipid forms of amphotericin B at a dose of 3-5 mg/kg/day may be used.
- Fluconazole at a dosage of 12 mg/kg/day is a reasonable alternative for patients who have not previously received fluconazole prophylaxis.
- The recommended duration of treatment for candidiasis is 2 weeks from the last negative blood culture and after the disappearance of clinical signs attributed to this infection.
- A lumbar puncture and fundus examination, preferably by an ophthalmologist, are recommended in neonates with normally sterile body fluids and/or with positive urine tests for Candida.
- Imaging of the genitourinary tract, liver and spleen should be performed if normally sterile body fluids remain positive for Candida.
- Echinocandins should be used with caution and in situations where resistance or toxicitylimits or prohibits the use of fluconazole or amphotericin B.
- Removal of the central line is strongly recommended.
- In our series, the average duration of treatment was 21 days.

Neonatal invasive candidiasis requires an adequate preventive strategy given the diagnostic difficulties of these infections and the mortality and morbidity they cause. Good practice guidelines for the management of candidal infections [24] are clear:

- In neonatal intensive care units with high rates of invasive candidiasis (>10%), fluconazole prophylaxis should be considered in neonates with a birth weight of <1000gat a dosage of 3-6 mg/kg twice weekly for 6 weeks.
- Nystatin 100,000 units 3 times daily for 6 weeks can be used orally in neonates with a birth weight <1500 g if fluconazole is not available or is resistant.

Mortality attributable to Candida infections ranges from 20 to 50% depending on the study andvaries according to the species, with morbidity primarily in the CNS and lungs [3]. Organ involvement (liver, eyes, lungs) is an important risk factor for secondary morbidity.

Bronchopulmonary dysplasia, retinopathy of prematurity, mental retardation is more common in preterm infants with neonatal Candida infection than in an identical population of uninfected preterm infants. An increased incidence of periventricular leukomalacia in preterm infants with invasive candidiasis has been reported in some studies [25] and in others not [26].In our series, the mortality rate was 31.9%, which is in line with the literature.

Conclusion

Neonatal systemic candidiasis is a real problem in the neonatal intensive care unit because of its diagnosis, which remains difficult in view of the non-specific clinical features, its treatment in view of the neonatal population, and its prognosis, which remains poor. Prophylaxis in at- risk neonates is important in order to reduce morbidity and mortality in neonatal intensive carecenters.

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